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# NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

#### 1. TECHNICAL FIELD

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with uses for these polynucleotides and proteins, for example in therapeutic, diagnostic and research methods.

#### 2. BACKGROUND

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs, chemokines, and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization-based cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity, for example, by virtue of their secreted nature in the case of leader sequence cloning, by virtue of their cell or tissue source in the case of PCR-based techniques, or by virtue of structural similarity to other genes of known biological activity.

Identified polynucleotide and polypeptide sequences have numerous applications in, for example, diagnostics, forensics, gene mapping; identification of mutations responsible for genetic disorders or other traits, to assess biodiversity, and to produce many other types of data and products dependent on DNA and amino acid sequences.

#### 3. SUMMARY OF THE INVENTION

The compositions of the present invention include novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies.

The compositions of the present invention additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides.

The present invention relates to a collection or library of at least one novel nucleic acid sequence assembled from expressed sequence tags (ESTs) isolated mainly by sequencing by hybridization (SBH), and in some cases, sequences obtained from one or more public databases. The invention relates also to the proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins. These nucleic acid sequences are designated as SEQ ID NO: 1-236 and 473-708. The polypeptides sequences are designated SEQ ID NO: 237-472 and 709-944. The nucleic acids and polypeptides are provided in the Sequence Listing. In the nucleic acids provided in the Sequence Listing, A is adenosine; C is cytosine; G is guanine; T is thymine; and N is any of the four bases. In the amino acids provided in the Sequence Listing, \* corresponds to the stop codon.

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The nucleic acid sequences of the present invention also include, nucleic acid sequences that hybridize to the complement of SEQ ID NO: 1-236 and 473-708 under stringent hybridization conditions; nucleic acid sequences which are allelic variants or species homologues of any of the nucleic acid sequences recited above, or nucleic acid sequences that encode a peptide comprising a specific domain or truncation of the peptides encoded by SEQ ID NO: 1-236 and 473-708. A polynucleotide comprising a nucleotide sequence having at least 90% identity to an identifying sequence of SEQ ID NO: 1-236 and 473-708 or a degenerate variant or fragment thereof. The identifying sequence can be 100 base pairs in length.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO:1-236 and 473-708. The sequence information can be a segment of any one of SEQ ID NO:1-236 and 473-708 that uniquely identifies or represents the sequence information of SEQ ID NO:1-236 and 473-708.

A collection as used in this application can be a collection of only one polynucleotide. The collection of sequence information or identifying information of each sequence can be provided on a nucleic acid array. In one embodiment, segments of sequence information is provided on a nucleic acid array to detect the polynucleotide that contains the segment. The array can be designed to detect full-match or mismatch to the polynucleotide that contains the segment. The collection can also be provided in a computer-readable format.

This invention also includes the reverse or direct complement of any of the nucleic acid sequences recited above; cloning or expression vectors containing the nucleic acid sequences; and host cells or organisms transformed with these expression vectors. Nucleic acid sequences (or their reverse or direct complements) according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology, such as use as hybridization probes, use as primers for PCR, use in an array, use in computer-readable media, use in sequencing

full-length genes, use for chromosome and gene mapping, use in the recombinant production of protein, and use in the generation of anti-sense DNA or RNA, their chemical analogs and the like.

In a preferred embodiment, the nucleic acid sequences of SEQ ID NO:1-236 and 473-708 or novel segments or parts of the nucleic acids of the invention are used as primers in expression assays that are well known in the art. In a particularly preferred embodiment, the nucleic acid sequences of SEQ ID NO:1-236 and 473-708 or novel segments or parts of the nucleic acids provided herein are used in diagnostics for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

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The isolated polynucleotides of the invention include, but are not limited to, a polynucleotide comprising any one of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708; a polynucleotide comprising any of the full length protein coding sequences of SEQ ID NO:1-236 and 473-708; and a polynucleotide comprising any of the nucleotide sequences of the mature protein coding sequences of SEQ ID NO:1-236 and 473-708. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent hybridization conditions to (a) the complement of any one of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708; (b) a nucleotide sequence encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotides recited above; (d) a polynucleotide which encodes a species homolog (e.g. orthologs) of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of any of the polypeptides comprising an amino acid sequence set forth in the Sequence Listing.

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising any of the amino acid sequences set forth in SEQ ID NO:237 – 472 or 709-944; or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides with biological activity that are encoded by (a) any of the polynucleotides having a nucleotide sequence set forth in SEQ ID NO:1-236 and 473-708; or (b) polynucleotides that hybridize to the complement of the polynucleotides of (a) under stringent hybridization conditions. Biologically or immunologically active variants of any of the polypeptide sequences in the Sequence Listing, and "substantial equivalents" thereof (e.g., with at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid sequence identity) that preferably retain biological activity are also contemplated. The polypeptides of the invention may be wholly or partially chemically synthesized but are preferably produced by recombinant means using the genetically engineered cells (e.g. host cells) of the invention.

The invention also provides compositions comprising a polypeptide of the invention. Polypeptide compositions of the invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The invention also provides host cells transformed or transfected with a polynucleotide of the invention.

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The invention also relates to methods for producing a polypeptide of the invention comprising growing a culture of the host cells of the invention in a suitable culture medium under conditions permitting expression of the desired polypeptide, and purifying the polypeptide from the culture or from the host cells. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Polynucleotides according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology. These techniques include use as hybridization probes, use as oligomers, or primers, for PCR, use for chromosome and gene mapping, use in the recombinant production of protein, and use in generation of anti-sense DNA or RNA, their chemical analogs and the like. For example, when the expression of an mRNA is largely restricted to a particular cell or tissue type, polynucleotides of the invention can be used as hybridization probes to detect the presence of the particular cell or tissue mRNA in a sample using, e.g., in situ hybridization.

In other exemplary embodiments, the polynucleotides are used in diagnostics as expressed sequence tags for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The polypeptides according to the invention can be used in a variety of conventional procedures and methods that are currently applied to other proteins. For example, a polypeptide of the invention can be used to generate an antibody that specifically binds the polypeptide. Such antibodies, particularly monoclonal antibodies, are useful for detecting or quantitating the polypeptide in tissue. The polypeptides of the invention can also be used as molecular weight markers, and as a food supplement.

Methods are also provided for preventing, treating, or ameliorating a medical condition which comprises the step of administering to a mammalian subject a therapeutically effective amount of a composition comprising a polypeptide of the present invention and a pharmaceutically acceptable carrier.

In particular, the polypeptides and polynucleotides of the invention can be utilized, for example, in methods for the prevention and/or treatment of disorders involving aberrant protein expression or biological activity.



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The present invention further relates to methods for detecting the presence of the polynucleotides or polypeptides of the invention in a sample. Such methods can, for example, be utilized as part of prognostic and diagnostic evaluation of disorders as recited herein and for the identification of subjects exhibiting a predisposition to such conditions. The invention provides a method for detecting the polynucleotides of the invention in a sample, comprising contacting the sample with a compound that binds to and forms a complex with the polynucleotide of interest for a period sufficient to form the complex and under conditions sufficient to form a complex and detecting the complex such that if a complex is detected, the polynucleotide of interest is detected. The invention also provides a method for detecting the polypeptides of the invention in a sample comprising contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex and detecting the formation of the complex such that if a complex is formed, the polypeptide is detected.

The invention also provides kits comprising polynucleotide probes and/or monoclonal antibodies, and optionally quantitative standards, for carrying out methods of the invention. Furthermore, the invention provides methods for evaluating the efficacy of drugs, and monitoring the progress of patients, involved in clinical trials for the treatment of disorders as recited above.

The invention also provides methods for the identification of compounds that modulate (i.e., increase or decrease) the expression or activity of the polynucleotides and/or polypeptides of the invention. Such methods can be utilized, for example, for the identification of compounds that can ameliorate symptoms of disorders as recited herein. Such methods can include, but are not limited to, assays for identifying compounds and other substances that interact with (e.g., bind to) the polypeptides of the invention. The invention provides a method for identifying a compound that binds to the polypeptides of the invention comprising contacting the compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and detecting the complex by detecting the reporter gene sequence expression such that if expression of the reporter gene is detected the compound the binds to a polypeptide of the invention is identified.

The methods of the invention also provides methods for treatment which involve the administration of the polynucleotides or polypeptides of the invention to individuals exhibiting symptoms or tendencies. In addition, the invention encompasses methods for treating diseases or disorders as recited herein comprising administering compounds and other substances that modulate the overall activity of the target gene products. Compounds and other substances can

effect such modulation either on the level of target gene/protein expression or target protein activity.

The polypeptides of the present invention and the polynucleotides encoding them are also useful for the same functions known to one of skill in the art as the polypeptides and polynucleotides to which they have homology (set forth in Table 2); for which they have a signature region (as set forth in Table 3); or for which they have homology to a gene family (as set forth in Table 4). If no homology is set forth for a sequence, then the polypeptides and polynucleotides of the present invention are useful for a variety of applications, as described herein, including use in arrays for detection.

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#### 4. DETAILED DESCRIPTION OF THE INVENTION

#### 4.1 DEFINITIONS.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

The term "active" refers to those forms of the polypeptide which retain the biologic and/or immunologic activities of any naturally occurring polypeptide. According to the invention, the terms "biologically active" or "biological activity" refer to a protein or peptide having structural, regulatory or biochemical functions of a naturally occurring molecule. Likewise "immunologically active" or "immunological activity" refers to the capability of the natural, recombinant or synthetic polypeptide to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The term "activated cells" as used in this application are those cells which are engaged in extracellular or intracellular membrane trafficking, including the export of secretory or enzymatic molecules as part of a normal or disease process.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence 5'-AGT-3' binds to the complementary sequence 3'-TCA-5'. Complementarity between two single-stranded molecules may be "partial" such that only some of the nucleic acids bind or it may be "complete" such that total complementarity exists between the single stranded molecules. The degree of complementarity between the nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands.

The term "embryonic stem cells (ES)" refers to a cell that can give rise to many differentiated cell types in an embryo or an adult, including the germ cells. The term "germ line stem cells (GSCs)" refers to stem cells derived from primordial stem cells that provide a steady

and continuous source of germ cells for the production of gametes. The term "primordial germ cells (PGCs)" refers to a small population of cells set aside from other cell lineages particularly from the yolk sac, mesenteries, or gonadal ridges during embryogenesis that have the potential to differentiate into germ cells and other cells. PGCs are the source from which GSCs and ES cells are derived The PGCs, the GSCs and the ES cells are capable of self-renewal. Thus these cells not only populate the germ line and give rise to a plurality of terminally differentiated cells that comprise the adult specialized organs, but are able to regenerate themselves.

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The term "expression modulating fragment," EMF, means a series of nucleotides which modulates the expression of an operably linked ORF or another EMF.

As used herein, a sequence is said to "modulate the expression of an operably linked sequence" when the expression of the sequence is altered by the presence of the EMF. EMFs include, but are not limited to, promoters, and promoter modulating sequences (inducible elements). One class of EMFs are nucleic acid fragments which induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

The terms "nucleotide sequence" or "nucleic acid" or "polynucleotide" or "oligonculeotide" are used interchangeably and refer to a heteropolymer of nucleotides or the sequence of these nucleotides. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. In the sequences herein A is adenine, C is cytosine, T is thymine, G is guanine and N is A, C, G or T (U). It is contemplated that where the polynucleotide is RNA, the T (thymine) in the sequences provided herein is substituted with U (uracil). Generally, nucleic acid segments provided by this invention may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid which is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon, or a eukaryotic gene.

The terms "oligonucleotide fragment" or a "polynucleotide fragment", "portion," or "segment" or "probe" or "primer" are used interchangeably and refer to a sequence of nucleotide residues which are at least about 5 nucleotides, more preferably at least about 7 nucleotides, more preferably at least about 11 nucleotides and most preferably at least about 17 nucleotides. The fragment is preferably less than about 500 nucleotides, preferably less than about 200 nucleotides, more preferably less than about 100 nucleotides, more preferably less than about 50 nucleotides and most preferably less than 30 nucleotides. Preferably the probe is from about 6 nucleotides to about 200 nucleotides, preferably from about 15 to about 50 nucleotides, more preferably from about 17 to 30

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nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can be used in polymerase chain reaction (PCR), various hybridization procedures or microarray procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A fragment or segment may uniquely identify each polynucleotide sequence of the present invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ ID NOs:1-20.

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Probes may, for example, be used to determine whether specific mRNA molecules are present in a cell or tissue or to isolate similar nucleic acid sequences from chromosomal DNA as described by Walsh et al. (Walsh, P.S. et al., 1992, PCR Methods Appl 1:241-250). They may be labeled by nick translation, Klenow fill-in reaction, PCR, or other methods well known in the art. Probes of the present invention, their preparation and/or labeling are elaborated in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY; or Ausubel, F.M. et al., 1989, Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, both of which are incorporated herein by reference in their entirety.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO:1-236 and 473-708. The sequence information can be a segment of any one of SEQ ID NO:1-236 and 473-708 that uniquely identifies or represents the sequence information of that sequence of SEQ ID NO:1-236 and 473-708. One such segment can be a twenty-mer nucleic acid sequence because the probability that a twenty-mer is fully matched in the human genome is 1 in 300. In the human genome, there are three billion base pairs in one set of chromosomes. Because 420 possible twenty-mers exist, there are 300 times more twenty-mers than there are base pairs in a set of human chromosomes. Using the same analysis, the probability for a seventeen-mer to be fully matched in the human genome is approximately 1 in 5. When these segments are used in arrays for expression studies, fifteenmer segments can be used. The probability that the fifteen-mer is fully matched in the expressed sequences is also approximately one in five because expressed sequences comprise less than approximately 5% of the entire genome sequence.

Similarly, when using sequence information for detecting a single mismatch, a segment can be a twenty-five mer. The probability that the twenty-five mer would appear in a human genome with a single mismatch is calculated by multiplying the probability for a full match  $(1 \div 4^{25})$  times the increased probability for mismatch at each nucleotide position (3 x 25). The probability that an eighteen mer with a single mismatch can be detected in an array for expression studies is approximately one in five. The probability that a twenty-mer with a single mismatch can be detected in a human genome is approximately one in five.

The term "open reading frame," ORF, means a series of nucleotide triplets coding for amino acids without any termination codons and is a sequence translatable into protein.

The terms "operably linked" or "operably associated" refer to functionally related nucleic acid sequences. For example, a promoter is operably associated or operably linked with a coding sequence if the promoter controls the transcription of the coding sequence. While operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements e.g. repressor genes are not contiguously linked to the coding sequence but still control transcription/translation of the coding sequence.

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The term "pluripotent" refers to the capability of a cell to differentiate into a number of differentiated cell types that are present in an adult organism. A pluripotent cell is restricted in its differentiation capability in comparison to a totipotent cell.

The terms "polypeptide" or "peptide" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or synthetic molecules. A polypeptide "fragment," "portion," or "segment" is a stretch of amino acid residues of at least about 5 amino acids, preferably at least about 7 amino acids, more preferably at least about 9 amino acids and most preferably at least about 17 or more amino acids. The peptide preferably is not greater than about 500 amino acids, more preferably less than 200 amino acids more preferably less than 150 amino acids and most preferably less than 100 amino acids. Preferably the peptide is from about 5 to about 200 amino acids. To be active, any polypeptide must have sufficient length to display biological and/or immunological activity.

The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation.

The term "translated protein coding portion" means a sequence which encodes for the full

The term "derivative" refers to polypeptides chemically modified by such techniques as ubiquitination, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of amino acids such as ornithine, which do not normally occur in human proteins.

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The term "variant" (or "analog") refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions, created using, e g., recombinant DNA techniques. Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, may be found by comparing the sequence of the particular polypeptide with that of homologous peptides and minimizing the number of amino acid sequence changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence.

Alternatively, recombinant variants encoding these same or similar polypeptides may be synthesized or selected by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes which produce various restriction sites, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic system. Mutations in the polynucleotide sequence may be reflected in the polypeptide or domains of other peptides added to the polypeptide to modify the properties of any part of the polypeptide, to change characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate.

Preferably, amino acid "substitutions" are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, *i.e.*, conservative amino acid replacements. "Conservative" amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophobicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. "Insertions" or "deletions" are preferably in the range of about 1 to 20 amino acids, more preferably 1 to 10 amino acids. The variation allowed may be experimentally determined by systematically making insertions, deletions, or substitutions of amino acids in a polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity.

Alternatively, where alteration of function is desired, insertions, deletions or non-conservative alterations can be engineered to produce altered polypeptides. Such alterations

can, for example, alter one or more of the biological functions or biochemical characteristics of the polypeptides of the invention. For example, such alterations may change polypeptide characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate. Further, such alterations can be selected so as to generate polypeptides that are better suited for expression, scale up and the like in the host cells chosen for expression. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

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The terms "purified" or "substantially purified" as used herein denotes that the indicated nucleic acid or polypeptide is present in the substantial absence of other biological macromolecules, e.g., polynucleotides, proteins, and the like. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight, more preferably at least 99% by weight, of the indicated biological macromolecules present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 daltons, can be present).

The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one other component (e.g., nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the nucleic acid or polypeptide is found in the presence of (if anything) only a solvent, buffer, ion, or other component normally present in a solution of the same. The terms "isolated" and "purified" do not encompass nucleic acids or polypeptides present in their natural source.

The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (e.g., microbial, insect, or mammalian) expression systems. "Microbial" refers to recombinant polypeptides or proteins made in bacterial or fungal (e.g., yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially free of native endogenous substances and unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, e.g., E. coli, will be free of glycosylation modifications; polypeptides or proteins expressed in yeast will have a glycosylation pattern in general different from those expressed in mammalian cells.

The term "recombinant expression vehicle or vector" refers to a plasmid or phage or virus or vector, for expressing a polypeptide from a DNA (RNA) sequence. An expression vehicle can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use

in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an amino terminal methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final product.

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The term "recombinant expression system" means host cells which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit extrachromosomally. Recombinant expression systems as defined herein will express heterologous polypeptides or proteins upon induction of the regulatory elements linked to the DNA segment or synthetic gene to be expressed. This term also means host cells which have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express polypeptides or proteins endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "secreted" includes a protein that is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence when it is expressed in a suitable host cell. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins that are transported across the membrane of the endoplasmic reticulum. "Secreted" proteins are also intended to include proteins containing non-typical signal sequences (e.g. Interleukin-1 Beta, see Krasney, P.A. and Young, P.R. (1992) Cytokine 4(2):134 -143) and factors released from damaged cells (e.g. Interleukin-1 Receptor Antagonist, see Arend, W.P. et. al. (1998) Annu. Rev. Immunol. 16:27-55)

Where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell. Such a sequence may be naturally present on the polypeptides of the present invention or provided from heterologous protein sources by recombinant DNA techniques.

The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Stringent conditions can include highly stringent conditions (i.e., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1X SSC/0.1% SDS at 68°C), and moderately stringent conditions (i.e., washing in 0.2X SSC/0.1% SDS at 42°C). Other exemplary hybridization conditions are described herein in the examples.

In instances of hybridization of deoxyoligonucleotides, additional exemplary stringent hybridization conditions include washing in 6X SSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligonucleotides), 48°C (for 17-base oligos), 55°C (for 20-base oligonucleotides), and 60°C (for 23-base oligonucleotides).

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As used herein, "substantially equivalent" can refer both to nucleotide and amino acid sequences, for example a mutant sequence, that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences. Typically, such a substantially equivalent sequence varies from one of those listed herein by no more than about 35% (i.e., the number of individual residue substitutions, additions, and/or deletions in a substantially equivalent sequence, as compared to the corresponding reference sequence, divided by the total number of residues in the substantially equivalent sequence is about 0.35 or less). Such a sequence is said to have 65% sequence identity to the listed sequence. In one embodiment, a substantially equivalent, e.g., mutant, sequence of the invention varies from a listed sequence by no more than 30% (70% sequence identity); in a variation of this embodiment, by no more than 25% (75% sequence identity); and in a further variation of this embodiment, by no more than 20% (80% sequence identity) and in a further variation of this embodiment, by no more than 10% (90% sequence identity) and in a further variation of this embodiment, by no more that 5% (95% sequence identity). Substantially equivalent, e.g., mutant, amino acid sequences according to the invention preferably have at least 80% sequence identity with a listed amino acid sequence, more preferably at least 90% sequence identity. Substantially equivalent nucleotide sequences of the invention can have lower percent sequence identities, taking into account, for example, the redundancy or degeneracy of the genetic code. Preferably, nucleotide sequence has at least about 65% identity, more preferably at least about 75% identity, and most preferably at least about 95% identity. For the purposes of the present invention, sequences having substantially equivalent biological activity and substantially equivalent expression characteristics are considered substantially equivalent. For the purposes of determining equivalence, truncation of the mature sequence (e.g., via a mutation which creates a spurious stop codon) should be disregarded. Sequence identity may be determined, e.g., using the Jotun Hein method (Hein, J. (1990) Methods Enzymol. 183:626-645). Identity between sequences can also be determined by other methods known in the art, e.g. by varying hybridization conditions.

The term "totipotent" refers to the capability of a cell to differentiate into all of the cell types of an adult organism.

The term "transformation" means introducing DNA into a suitable host cell so that the DNA is replicable, either as an extrachromosomal element, or by chromosomal integration. The term "transfection" refers to the taking up of an expression vector by a suitable host cell, whether or not any coding sequences are in fact expressed. The term "infection" refers to the introduction of nucleic acids into a suitable host cell by use of a virus or viral vector.

As used herein, an "uptake modulating fragment," UMF, means a series of nucleotides which mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified using known UMFs as a target sequence or target motif with the computer-based systems described below. The presence and activity of a UMF can be confirmed by attaching the suspected UMF to a marker sequence. The resulting nucleic acid molecule is then incubated with an appropriate host under appropriate conditions and the uptake of the marker sequence is determined. As described above, a UMF will increase the frequency of uptake of a linked marker sequence.

Each of the above terms is meant to encompass all that is described for each, unless the context dictates otherwise.

# 4.2 NUCLEIC ACIDS OF THE INVENTION

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Nucleotide sequences of the invention are set forth in the Sequence Listing.

The isolated polynucleotides of the invention include a polynucleotide comprising the nucleotide sequences of SEQ ID NO:1-236 and 473-708; a polynucleotide encoding any one of the peptide sequences of SEQ ID NO:237-472 and 709-944; and a polynucleotide comprising the nucleotide sequence encoding the mature protein coding sequence of the polypeptides of any one of SEQ ID NO:237-472 and 709-944. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent conditions to (a) the complement of any of the nucleotides sequences of SEQ ID NO:1-236 and 473-708; (b) nucleotide sequences encoding any one of the amino acid sequences set forth in the Sequence Listing as SEQ ID NO:237-472 and 709-944; (c) a polynucleotide which is an allelic variant of any polynucleotide recited above; (d) a polynucleotide which encodes a species homolog of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of the polypeptides of SEQ ID NO:237-472 and 709-944. Domains of interest may depend on the nature of the encoded polypeptide; e.g., domains in receptor-like polypeptides include ligand-binding, extracellular, transmembrane, or cytoplasmic domains, or combinations thereof; domains in immunoglobulin-like proteins include the variable immunoglobulin-like domains; domains in enzyme-like polypeptides include catalytic and

substrate binding domains; and domains in ligand polypeptides include receptor-binding domains.

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The polynucleotides of the invention include naturally occurring or wholly or partially synthetic DNA, e.g., cDNA and genomic DNA, and RNA, e.g., mRNA. The polynucleotides may include all of the coding region of the cDNA or may represent a portion of the coding region of the cDNA.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. Further 5' and 3' sequence can be obtained using methods known in the art. For example, full length cDNA or genomic DNA that corresponds to any of the polynucleotides of SEQ ID NO:1-236 and 473-708 can be obtained by screening appropriate cDNA or genomic DNA libraries under suitable hybridization conditions using any of the polynucleotides of SEQ ID NO:1-236 and 473-708 or a portion thereof as a probe. Alternatively, the polynucleotides of SEQ ID NO:1-236 and 473-708 may be used as the basis for suitable primer(s) that allow identification and/or amplification of genes in appropriate genomic DNA or cDNA libraries.

The nucleic acid sequences of the invention can be assembled from ESTs and sequences (including cDNA and genomic sequences) obtained from one or more public databases, such as dbEST, gbpri, and UniGene. The EST sequences can provide identifying sequence information, representative fragment or segment information, or novel segment information for the full-length gene.

The polynucleotides of the invention also provide polynucleotides including nucleotide sequences that are substantially equivalent to the polynucleotides recited above. Polynucleotides according to the invention can have, e.g., at least about 65%, at least about 70%, at least about 75%, at least about 80%, more typically at least about 90%, and even more typically at least about 95%, sequence identity to a polynucleotide recited above.

Included within the scope of the nucleic acid sequences of the invention are nucleic acid sequence fragments that hybridize under stringent conditions to any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708, or complements thereof, which fragment is greater than about 5 nucleotides, preferably 7 nucleotides, more preferably greater than 9 nucleotides and most preferably greater than 17 nucleotides. Fragments of, e.g. 15, 17, or 20 nucleotides or more that are selective for (i.e. specifically hybridize to any one of the polynucleotides of the invention) are contemplated. Probes capable of specifically hybridizing to a polynucleotide can

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differentiate polynucleotide sequences of the invention from other polynucleotide sequences in the same family of genes or can differentiate human genes from genes of other species, and are preferably based on unique nucleotide sequences.

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The sequences falling within the scope of the present invention are not limited to these specific sequences, but also include allelic and species variations thereof. Allelic and species variations can be routinely determined by comparing the sequence provided SEQ ID NO:1-236 and 473-708, a representative fragment thereof, or a nucleotide sequence at least 90% identical, preferably 95% identical, to SEQ ID NO:1-236 and 473-708 with a sequence from another isolate of the same species. Furthermore, to accommodate codon variability, the invention includes nucleic acid molecules coding for the same amino acid sequences as do the specific ORFs disclosed herein. In other words, in the coding region of an ORF, substitution of one codon for another codon that encodes the same amino acid is expressly contemplated.

The nearest neighbor or homology result for the nucleic acids of the present invention, including SEQ ID NO:1-236 and 473-708, can be obtained by searching a database using an algorithm or a program. Preferably, a BLAST which stands for Basic Local Alignment Search Tool is used to search for local sequence alignments (Altshul, S.F. J Mol. Evol. 36 290-300 (1993) and Altschul S.F. et al. J. Mol. Biol. 21:403-410 (1990)). Alternatively a FASTA version 3 search against Genpept, using Fastxy algorithm.

Species homologs (or orthologs) of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

The nucleic acid sequences of the invention are further directed to sequences which encode variants of the described nucleic acids. These amino acid sequence variants may be prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant polynucleotide. There are two variables in the construction of amino acid sequence variants: the location of the mutation and the nature of the mutation. Nucleic acids encoding the amino acid sequence variants are preferably constructed by mutating the polynucleotide to encode an amino acid sequence that does not occur in nature. These nucleic acid alterations can be made at sites that differ in the nucleic acids from different species (variable positions) or in highly conserved regions (constant regions). Sites at such locations

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will typically be modified in series, e.g., by substituting first with conservative choices (e.g., hydrophobic amino acid to a different hydrophobic amino acid) and then with more distant choices (e.g., hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be made at the target site. Amino acid sequence deletions generally range from about 1 to 30 residues, preferably about 1 to 10 residues, and are typically contiguous. Amino acid insertions include amino- and/or carboxyl-terminal fusions ranging in length from one to one hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of terminal insertions include the heterologous signal sequences necessary for secretion or for intracellular targeting in different host cells and sequences such as FLAG or poly-histidine sequences useful for purifying the expressed protein.

In a preferred method, polynucleotides encoding the novel amino acid sequences are changed via site-directed mutagenesis. This method uses oligonucleotide sequences to alter a polynucleotide to encode the desired amino acid variant, as well as sufficient adjacent nucleotides on both sides of the changed amino acid to form a stable duplex on either side of the site of being changed. In general, the techniques of site-directed mutagenesis are well known to those of skill in the art and this technique is exemplified by publications such as, Edelman et al., DNA 2:183 (1983). A versatile and efficient method for producing site-specific changes in a polynucleotide sequence was published by Zoller and Smith, Nucleic Acids Res. 10:6487-6500 (1982). PCR may also be used to create amino acid sequence variants of the novel nucleic acids. When small amounts of template DNA are used as starting material, primer(s) that differs slightly in sequence from the corresponding region in the template DNA can generate the desired amino acid variant. PCR amplification results in a population of product DNA fragments that differ from the polynucleotide template encoding the polypeptide at the position specified by the primer. The product DNA fragments replace the corresponding region in the plasmid and this gives a polynucleotide encoding the desired amino acid variant.

A further technique for generating amino acid variants is the cassette mutagenesis technique described in Wells et al., *Gene* 34:315 (1985); and other mutagenesis techniques well known in the art, such as, for example, the techniques in Sambrook et al., supra, and *Current Protocols in Molecular Biology*, Ausubel et al. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be used in the practice of the invention for the cloning and expression of these novel nucleic acids. Such DNA sequences include those which are capable of hybridizing to the appropriate novel nucleic acid sequence under stringent conditions.

Polynucleotides encoding preferred polypeptide truncations of the invention can be used to generate polynucleotides encoding chimeric or fusion proteins comprising one or more domains of the invention and heterologous protein sequences.

The polynucleotides of the invention additionally include the complement of any of the polynucleotides recited above. The polynucleotide can be DNA (genomic, cDNA, amplified, or synthetic) or RNA. Methods and algorithms for obtaining such polynucleotides are well known to those of skill in the art and can include, for example, methods for determining hybridization conditions that can routinely isolate polynucleotides of the desired sequence identities.

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In accordance with the invention, polynucleotide sequences comprising the mature protein coding sequences corresponding to any one of SEQ ID NO:1-236 and 473-708, or functional equivalents thereof, may be used to generate recombinant DNA molecules that direct the expression of that nucleic acid, or a functional equivalent thereof, in appropriate host cells. Also included are the cDNA inserts of any of the clones identified herein.

A polynucleotide according to the invention can be joined to any of a variety of other nucleotide sequences by well-established recombinant DNA techniques (see Sambrook J et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY). Useful nucleotide sequences for joining to polynucleotides include an assortment of vectors, e.g., plasmids, cosmids, lambda phage derivatives, phagemids, and the like, that are well known in the art. Accordingly, the invention also provides a vector including a polynucleotide of the invention and a host cell containing the polynucleotide. In general, the vector contains an origin of replication functional in at least one organism, convenient restriction endonuclease sites, and a selectable marker for the host cell. Vectors according to the invention include expression vectors, replication vectors, probe generation vectors, and sequencing vectors. A host cell according to the invention can be a prokaryotic or eukaryotic cell and can be a unicellular organism or part of a multicellular organism.

The present invention further provides recombinant constructs comprising a nucleic acid having any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708 or a fragment thereof or any other polynucleotides of the invention. In one embodiment, the recombinant constructs of the present invention comprise a vector, such as a plasmid or viral vector, into which a nucleic acid having any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708 or a fragment thereof is inserted, in a forward or reverse orientation. In the case of a vector comprising one of the ORFs of the present invention, the vector may further comprise regulatory sequences, including for example, a promoter, operably linked to the ORF. Large numbers of suitable vectors and promoters are known to those of skill in the art and are commercially available for generating the recombinant constructs of the present invention. The following vectors are

provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, PXTI, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia).

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The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al., Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, and trc. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), a-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an amino terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product. Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for

transformation include E. coli, Bacillus subtilis, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM 1 (Promega Biotech, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced or derepressed by appropriate means (e.g., temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Polynucleotides of the invention can also be used to induce immune responses. For example, as described in Fan et al., *Nat. Biotech.* 17:870-872 (1999), incorporated herein by reference, nucleic acid sequences encoding a polypeptide may be used to generate antibodies against the encoded polypeptide following topical administration of naked plasmid DNA or following injection, and preferably intramuscular injection of the DNA. The nucleic acid sequences are preferably inserted in a recombinant expression vector and may be in the form of naked DNA.

#### **4.3 ANTISENSE**

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Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1-236 and 473-708, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein, e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of a protein of any of SEQ ID NO:237-472 and 709-944 or antisense nucleic acids complementary to a nucleic acid sequence of SEQ ID NO:1-236 and 473-708 are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence of the invention. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence of the invention. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (i.e., also referred to as 5' and 3' untranslated regions).

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Given the coding strand sequences encoding a nucleic acid disclosed herein (e.g., SEQ ID NO:1-236 and 473-708), antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of a mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of a mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of a mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used.

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, 25 inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, 30 queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the 35

inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

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The antisense nucleic acid molecules of the invention are typically administered to a subject or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a protein according to the invention to thereby inhibit expression of the protein, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res* 15: 6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res* 15: 6131-6148) or a chimeric RNA -DNA analogue (Inoue *et al.* (1987) *FEBS Lett* 215: 327-330).

# 4.4 RIBOZYMES AND PNA MOIETIES

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as a mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach (1988) Nature 334:585-591)) can be used to catalytically cleave a mRNA transcripts to thereby inhibit translation of a mRNA. A ribozyme having specificity for a nucleic acid of the invention can be designed based upon the nucleotide sequence of a DNA disclosed herein (i.e., SEQ ID NO:1-236 and 473-708). For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in

which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a SECX-encoding mRNA. See, e.g., Cech et al. U.S. Pat. No. 4,987,071; and Cech et al. U.S. Pat. No. 5,116,742. Alternatively, SECX mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel et al., (1993) Science 261:1411-1418.

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Alternatively, gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region (e.g., promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene in target cells. See generally, Helene. (1991) Anticancer Drug Des. 6: 569-84; Helene. et al. (1992) Ann. N.Y. Acad. Sci. 660:27-36; and Maher (1992) Bioassays 14: 807-15.

In various embodiments, the nucleic acids of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup et al. (1996) Bioorg Med Chem 4: 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996) above; Perry-O'Keefe et al. (1996) PNAS 93: 14670-675.

PNAs of the invention can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs of the invention can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup B. (1996) above); or as probes or primers for DNA sequence and hybridization (Hyrup et al. (1996), above; Perry-O'Keefe (1996), above).

In another embodiment, PNAs of the invention can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA

portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup (1996) above). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996) above and Finn et al. (1996) Nucl Acids Res 24: 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, e.g., 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA (Mag et al. (1989) Nucl Acid Res 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al. (1996) above). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. See, Petersen et al. (1975) Bioorg Med Chem Lett 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, etc.

#### 4.5 HOSTS

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The present invention further provides host cells genetically engineered to contain the polynucleotides of the invention. For example, such host cells may contain nucleic acids of the invention introduced into the host cell using known transformation, transfection or infection methods. The present invention still further provides host cells genetically engineered to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell.

Knowledge of nucleic acid sequences allows for modification of cells to permit, or increase, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express

the polypeptide at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the encoding sequences. See, for example, PCT International Publication No. WO94/12650, PCT International Publication No. WO92/20808, and PCT International Publication No. WO91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the coding sequence, amplification of the marker DNA by standard selection methods results in coamplification of the desired protein coding sequences in the cells.

The host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated transfection, or electroporation (Davis, L. et al., *Basic Methods in Molecular Biology* (1986)). The host cells containing one of the polynucleotides of the invention, can be used in conventional manners to produce the gene product encoded by the isolated fragment (in the case of an ORF) or can be used to produce a heterologous protein under the control of the EMF.

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Any host/vector system can be used to express one or more of the ORFs of the present invention. These include, but are not limited to, eukaryotic hosts such as HeLa cells, Cv-1 cell, COS cells, 293 cells, and Sf9 cells, as well as prokaryotic host such as *E. coli* and *B. subtilis*. The most preferred cells are those which do not normally express the particular polypeptide or protein or which expresses the polypeptide or protein at low natural level. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., in Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, New York (1989), the disclosure of which is hereby incorporated by reference.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell 23:175 (1981). Other cell lines capable of expressing a compatible vector are, for example, the C127, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK,

HL-60, U937, HaK or Jurkat cells. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Recombinant polypeptides and proteins produced in bacterial culture are usually isolated by initial extraction from cell pellets, followed by one or more salting-out, aqueous ion exchange or size exclusion chromatography steps. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or insects or in prokaryotes such as bacteria. Potentially suitable yeast strains include Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces strains, Candida, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include Escherichia coli, Bacillus subtilis, Salmonella typhimurium, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequence include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the

protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

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The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, e.g., inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the host cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

#### 4.6 POLYPEPTIDES OF THE INVENTION

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising: the amino acid sequences set forth as any one of SEQ ID NO:237-472 and 709-944 or an amino acid sequence encoded by any one of the nucleotide sequences SEQ ID NO:1-236 and 473-708 or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides preferably with biological or immunological activity that are encoded by: (a) a polynucleotide having any one of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708 or (b) polynucleotides encoding any one of the amino acid sequences set forth

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as SEQ ID NO:237-472 and 709-944 or (c) polynucleotides that hybridize to the complement of the polynucleotides of either (a) or (b) under stringent hybridization conditions. The invention also provides biologically active or immunologically active variants of any of the amino acid sequences set forth as SEQ ID NO:237-472 and 709-944 or the corresponding full length or mature protein; and "substantial equivalents" thereof (e.g., with at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, typically at least about 95%, more typically at least about 98%, or most typically at least about 99% amino acid identity) that retain biological activity. Polypeptides encoded by allelic variants may have a similar, increased, or decreased activity compared to polypeptides comprising SEQ ID NO:237-472 and 709-944.

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Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H. U. Saragovi, et al., Bio/Technology 10, 773-778 (1992) and in R. S. McDowell, et al., J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites.

The present invention also provides both full-length and mature forms (for example, without a signal sequence or precursor sequence) of the disclosed proteins. The protein coding sequence is identified in the sequence listing by translation of the disclosed nucleotide sequences. The mature form of such protein may be obtained by expression of a full-length polynucleotide in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein is also determinable from the amino acid sequence of the full-length form. Where proteins of the present invention are membrane bound, soluble forms of the proteins are also provided. In such forms, part or all of the regions causing the proteins to be membrane bound are deleted so that the proteins are fully secreted from the cell in which they are expressed.

Protein compositions of the present invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The present invention further provides isolated polypeptides encoded by the nucleic acid fragments of the present invention or by degenerate variants of the nucleic acid fragments of the present invention. By "degenerate variant" is intended nucleotide fragments which differ from a nucleic acid fragment of the present invention (e.g., an ORF) by nucleotide sequence but, due to the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic acid fragments of the present invention are the ORFs that encode proteins.

A variety of methodologies known in the art can be utilized to obtain any one of the isolated polypeptides or proteins of the present invention. At the simplest level, the amino acid sequence can be synthesized using commercially available peptide synthesizers. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. This technique is particularly useful in producing small peptides and fragments of larger polypeptides. Fragments are useful, for example, in generating antibodies against the native polypeptide. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The polypeptides and proteins of the present invention can alternatively be purified from cells which have been altered to express the desired polypeptide or protein. As used herein, a cell is said to be altered to express a desired polypeptide or protein when the cell, through genetic manipulation, is made to produce a polypeptide or protein which it normally does not produce or which the cell normally produces at a lower level. One skilled in the art can readily adapt procedures for introducing and expressing either recombinant or synthetic sequences into eukaryotic or prokaryotic cells in order to generate a cell which produces one of the polypeptides or proteins of the present invention.

The invention also relates to methods for producing a polypeptide comprising growing a culture of host cells of the invention in a suitable culture medium, and purifying the protein from the cells or the culture in which the cells are grown. For example, the methods of the invention include a process for producing a polypeptide in which a host cell containing a suitable expression vector that includes a polynucleotide of the invention is cultured under conditions that allow expression of the encoded polypeptide. The polypeptide can be recovered from the culture, conveniently from the culture medium, or from a lysate prepared from the host cells and further purified. Preferred embodiments include those in which the protein produced by such process is a full length or mature form of the protein.

In an alternative method, the polypeptide or protein is purified from bacterial cells which naturally produce the polypeptide or protein. One skilled in the art can readily follow known methods for isolating polypeptides and proteins in order to obtain one of the isolated polypeptides or proteins of the present invention. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immuno-affinity chromatography. See, e.g., Scopes, Protein Purification: Principles and Practice, Springer-Verlag (1994); Sambrook, et al., in Molecular Cloning: A Laboratory Manual; Ausubel et al., Current Protocols in Molecular Biology. Polypeptide fragments that

retain biological/immunological activity include fragments comprising greater than about 100 amino acids, or greater than about 200 amino acids, and fragments that encode specific protein domains.

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The purified polypeptides can be used in *in vitro* binding assays which are well known in the art to identify molecules which bind to the polypeptides. These molecules include but are not limited to, for e.g., small molecules, molecules from combinatorial libraries, antibodies or other proteins. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

In addition, the peptides of the invention or molecules capable of binding to the peptides may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for SEQ ID NO:237-472 and 709-944.

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications, in the peptide or DNA sequence, can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Pat. No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein. Regions of the protein that are important for the protein function can be determined by various methods known in the art including the alanine-scanning method which involved systematic substitution of single or strings of amino acids with alanine, followed by testing the resulting alanine-containing variant for biological activity. This type of analysis determines the importance of the substituted amino acid(s) in biological activity. Regions of the protein that are important for protein function may be determined by the eMATRIX program.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and are useful for screening or other immunological

methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are encompassed by the present invention.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, Calif., U.S.A. (the MaxBat<sup>TM</sup> kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

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The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl<sup>TM</sup> or Cibacrom blue 3GA Sepharose<sup>TM</sup>; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX), or as a His tag. Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, Mass.), Pharmacia (Piscataway, N.J.) and Invitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("FLAG®") is commercially available from Kodak (New Haven, Conn.).

Finally, one or more reverse-phase high performance liquid chromatography (RP- HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The polypeptides of the invention include analogs (variants). This embraces fragments, as well as peptides in which one or more amino acids has been deleted, inserted, or substituted. Also, analogs of the polypeptides of the invention embrace fusions of the polypeptides or modifications of the polypeptides of the invention, wherein the polypeptide or analog is fused to another moiety or moieties, e.g., targeting moiety or another therapeutic agent. Such analogs may exhibit improved properties such as activity and/or stability. Examples of moieties which may be fused to the polypeptide or an analog include, for example, targeting moieties which provide for the delivery of polypeptide to pancreatic cells, e.g., antibodies to pancreatic cells, antibodies to immune cells such as T-cells, monocytes, dendritic cells, granulocytes, etc., as well as receptor and ligands expressed on pancreatic or immune cells. Other moieties which may be fused to the polypeptide include therapeutic agents which are used for treatment, for example, immunosuppressive drugs such as cyclosporin, SK506, azathioprine, CD3 antibodies and steroids. Also, polypeptides may be fused to immune modulators, and other cytokines such as alpha or beta interferon.

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# 4.6.1 DETERMINING POLYPEPTIDE AND POLYNUCLEOTIDE IDENTITY AND SIMILARITY

Preferred identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in computer programs including, but are not limited to, the GCG program package, including GAP (Devereux, J., et al., Nucleic Acids Research 12(1):387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, BLASTX, FASTA (Altschul, S.F. et al., J. Molec. Biol. 215:403-410 (1990), PSI-BLAST (Altschul S.F. et al., Nucleic Acids Res. vol. 25, pp. 3389-3402, herein incorporated by reference), eMatrix software (Wu et al., J. Comp. Biol., Vol. 6, pp. 219-235 (1999), herein incorporated by reference), eMotif software (Nevill-Manning et al, ISMB-97, Vol. 4, pp. 202-209, herein incorporated by reference), pFam software (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1), pp. 320-322 (1998), herein incorporated by reference) and the Kyte-Doolittle hydrophobocity prediction algorithm (J. Mol Biol, 157, pp. 105-31 (1982), incorporated herein by reference). The BLAST programs are publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul, S., et al. NCB NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990).

# 4.7 CHIMERIC AND FUSION PROTEINS

The invention also provides chimeric or fusion proteins. As used herein, a "chimeric protein" or "fusion protein" comprises a polypeptide of the invention operatively linked to

another polypeptide. Within a fusion protein the polypeptide according to the invention can correspond to all or a portion of a protein according to the invention. In one embodiment, a fusion protein comprises at least one biologically active portion of a protein according to the invention. In another embodiment, a fusion protein comprises at least two biologically active portions of a protein according to the invention. Within the fusion protein, the term "operatively linked" is intended to indicate that the polypeptide according to the invention and the other polypeptide are fused in-frame to each other. The polypeptide can be fused to the N-terminus or C-terminus.

For example, in one embodiment a fusion protein comprises a polypeptide according to the invention operably linked to the extracellular domain of a second protein.

In another embodiment, the fusion protein is a GST-fusion protein in which the polypeptide sequences of the invention are fused to the C-terminus of the GST (i.e., glutathione S-transferase) sequences.

In another embodiment, the fusion protein is an immunoglobulin fusion protein in which the polypeptide sequences according to the invention comprise one or more domains fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand and a protein of the invention on the surface of a cell, to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion proteins can be used to affect the bioavailability of a cognate ligand. Inhibition of the ligand/protein interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, *e,g.*, cancer as well as modulating (*e.g.*, promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies in a subject, to purify ligands, and in screening assays to identify molecules that inhibit the interaction of a polypeptide of the invention with a ligand.

A chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, e.g., by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers.

Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for

example, Ausubel et al. (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the protein of the invention.

#### 4.8 GENE THERAPY

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Mutations in the polynucleotides of the invention gene may result in loss of normal function of the encoded protein. The invention thus provides gene therapy to restore normal activity of the polypeptides of the invention; or to treat disease states involving polypeptides of the invention. Delivery of a functional gene encoding polypeptides of the invention to appropriate cells is effected ex vivo, in situ, or in vivo by use of vectors, and more particularly viral vectors (e.g., adenovirus, adeno-associated virus, or a retrovirus), or ex vivo by use of physical DNA transfer methods (e.g., liposomes or chemical treatments). See, for example, Anderson, Nature, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, Science, 244: 1275-1281 (1989); Verma, Scientific American: 68-84 (1990); and Miller, Nature, 357: 455-460 (1992). Introduction of any one of the nucleotides of the present invention or a gene encoding the polypeptides of the present invention can also be accomplished with extrachromosomal substrates (transient expression) or artificial chromosomes (stable expression). Cells may also be cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes. Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

Other methods inhibiting expression of a protein include the introduction of antisense molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in the art. Further, the polypeptides of the present invention can be inhibited by using targeted deletion methods, or the insertion of a negative regulatory element such as a silencer, which is tissue specific.

The present invention still further provides cells genetically engineered *in vivo* to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in

the cell. These methods can be used to increase or decrease the expression of the polynucleotides of the present invention.

Knowledge of DNA sequences provided by the invention allows for modification of cells to permit, increase, or decrease, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the protein at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the desired protein encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the desired protein coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, e.g., inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are

added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

### 4.9 TRANSGENIC ANIMALS

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In preferred methods to determine biological functions of the polypeptides of the invention in vivo, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of a promoter of the polynucleotides of the invention is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous

promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

The polynucleotides of the present invention also make possible the development, through, e.g., homologous recombination or knock out strategies, of animals that fail to express polypeptides of the invention or that express a variant polypeptide. Such animals are useful as models for studying the *in vivo* activities of polypeptide as well as for studying modulators of the polypeptides of the invention.

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In preferred methods to determine biological functions of the polypeptides of the invention *in vivo*, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of the polynucleotides of the invention promoter is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

#### 4.10 USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA). The mechanism underlying the particular condition or pathology will dictate whether the

polypeptides of the invention, the polynucleotides of the invention or modulators (activators or inhibitors) thereof would be beneficial to the subject in need of treatment. Thus, "therapeutic compositions of the invention" include compositions comprising isolated polynucleotides (including recombinant DNA molecules, cloned genes and degenerate variants thereof) or polypeptides of the invention (including full length protein, mature protein and truncations or domains thereof), or compounds and other substances that modulate the overall activity of the target gene products, either at the level of target gene/protein expression or target protein activity. Such modulators include polypeptides, analogs, (variants), including fragments and fusion proteins, antibodies and other binding proteins; chemical compounds that directly or indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); antisense polynucleotides and polynucleotides suitable for triple helix formation; and in particular antibodies or other binding partners that specifically recognize one or more epitopes of the polypeptides of the invention.

The polypeptides of the present invention may likewise be involved in cellular activation or in one of the other physiological pathways described herein.

#### 4.10.1 RESEARCH USES AND UTILITIES

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The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding polypeptide is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

# 4.10.2 NUTRITIONAL USES

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Polynucleotides and polypeptides of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the polypeptide or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the polypeptide or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

# 4.10.3 CYTOKINE AND CELL PROLIFERATION/DIFFERENTIATION ACTIVITY

A polypeptide of the present invention may exhibit activity relating to cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient

confirmation of cytokine activity. The activity of therapeutic compositions of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e, CMK, HUVEC, and Caco. Therapeutic compositions of the invention can be used in the following:

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Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., I. Immunol. 149:3778-3783, 1992; Bowman et al., I. Immunol. 152:1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A. M. and Shevach, E. M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human interleukin-γ, Schreiber, R. D. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L. S. and Lipsky, P. E. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6--Nordan, R. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Aced. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11--Bennett, F., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9--Ciarletta, A., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W Strober,

Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### 4.10.4 STEM CELL GROWTH FACTOR ACTIVITY

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A polypeptide of the present invention may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells, hematopoietic stem cells and/or germ line stem cells. Administration of the polypeptide of the invention to stem cells *in vivo* or *ex vivo* is expected to maintain and expand cell populations in a totipotential or pluripotential state which would be useful for re-engineering damaged or diseased tissues, transplantation, manufacture of bio-pharmaceuticals and the development of bio-sensors. The ability to produce large quantities of human cells has important working applications for the production of human proteins which currently must be obtained from non-human sources or donors, implantation of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow, skin, cartilage, tendons, bone, muscle (including cardiac muscle), blood vessels, cornea, neural cells, gastrointestinal cells and others; and organs for transplantation such as kidney, liver, pancreas (including islet cells), heart and lung.

It is contemplated that multiple different exogenous growth factors and/or cytokines may be administered in combination with the polypeptide of the invention to achieve the desired effect, including any of the growth factors listed herein, other stem cell maintenance factors, and specifically including stem cell factor (SCF), leukemia inhibitory factor (LIF), Flt-3 ligand (Flt-3L), any of the interleukins, recombinant soluble IL-6 receptor fused to IL-6, macrophage inflammatory protein 1-alpha (MIP-1-alpha), G-CSF, GM-CSF, thrombopoietin (TPO), platelet factor 4 (PF-4), platelet-derived growth factor (PDGF), neural growth factors and basic fibroblast growth factor (bFGF).

Since totipotent stem cells can give rise to virtually any mature cell type, expansion of these cells in culture will facilitate the production of large quantities of mature cells. Techniques for culturing stem cells are known in the art and administration of polypeptides of the invention, optionally with other growth factors and/or cytokines, is expected to enhance the survival and proliferation of the stem cell populations. This can be accomplished by direct administration of the polypeptide of the invention to the culture medium. Alternatively, stroma cells transfected with a polynucleotide that encodes for the polypeptide of the invention can be used as a feeder

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layer for the stem cell populations in culture or in vivo. Stromal support cells for feeder layers may include embryonic bone marrow fibroblasts, bone marrow stromal cells, fetal liver cells, or cultured embryonic fibroblasts (see U.S. Patent No. 5,690,926).

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Stem cells themselves can be transfected with a polynucleotide of the invention to induce autocrine expression of the polypeptide of the invention. This will allow for generation of undifferentiated totipotential/pluripotential stem cell lines that are useful as is or that can then be differentiated into the desired mature cell types. These stable cell lines can also serve as a source of undifferentiated totipotential/pluripotential mRNA to create cDNA libraries and templates for polymerase chain reaction experiments. These studies would allow for the isolation and identification of differentially expressed genes in stem cell populations that regulate stem cell proliferation and/or maintenance.

Expansion and maintenance of totipotent stem cell populations will be useful in the treatment of many pathological conditions. For example, polypeptides of the present invention may be used to manipulate stem cells in culture to give rise to neuroepithelial cells that can be used to augment or replace cells damaged by illness, autoimmune disease, accidental damage or genetic disorders. The polypeptide of the invention may be useful for inducing the proliferation of neural cells and for the regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders which involve degeneration, death or trauma to neural cells or nerve tissue. In addition, the expanded stem cell populations can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or implantation.

Expression of the polypeptide of the invention and its effect on stem cells can also be manipulated to achieve controlled differentiation of the stem cells into more differentiated cell types. A broadly applicable method of obtaining pure populations of a specific differentiated cell type from undifferentiated stem cell populations involves the use of a cell-type specific promoter driving a selectable marker. The selectable marker allows only cells of the desired type to survive. For example, stem cells can be induced to differentiate into cardiomyocytes (Wobus et al., Differentiation, 48: 173-182, (1991); Klug et al., J. Clin. Invest., 98(1): 216-224, (1998)) or skeletal muscle cells (Browder, L. W. In: *Principles of Tissue Engineering eds*. Lanza et al., Academic Press (1997)). Alternatively, directed differentiation of stem cells can be accomplished by culturing the stem cells in the presence of a differentiation factor such as retinoic acid and an antagonist of the polypeptide of the invention which would inhibit the effects of endogenous stem cell factor activity and allow differentiation to proceed.

In vitro cultures of stem cells can be used to determine if the polypeptide of the invention exhibits stem cell growth factor activity. Stem cells are isolated from any one of various cell

sources (including hematopoietic stem cells and embryonic stem cells) and cultured on a feeder layer, as described by Thompson et al. Proc. Natl. Acad. Sci, U.S.A., 92: 7844-7848 (1995), in the presence of the polypeptide of the invention alone or in combination with other growth factors or cytokines. The ability of the polypeptide of the invention to induce stem cells proliferation is determined by colony formation on semi-solid support e.g. as described by Bernstein et al., Blood, 77: 2316-2321 (1991).

# 4.10.5 HEMATOPOIESIS REGULATING ACTIVITY

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A polypeptide of the present invention may be involved in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell disorders. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

Therapeutic compositions of the invention can be used in the following:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M. G. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells 5 with high proliferative potential, McNiece, I. K. and Briddell, R. A. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, N.Y. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R. E. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, N.Y. 1994; Long term bone marrow cultures in the presence of 10 stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, N.Y. 1994; Long term culture initiating cell assay, Sutherland, H. J. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, N.Y. 1994.

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# 4.10.6 TISSUE GROWTH ACTIVITY

A polypeptide of the present invention also may be involved in bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as in wound healing and tissue repair and replacement, and in healing of burns, incisions and ulcers.

A polypeptide of the present invention which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Compositions of a polypeptide, antibody, binding partner, or other modulator of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A polypeptide of this invention may also be involved in attracting bone-forming cells, stimulating growth of bone-forming cells, or inducing differentiation of progenitors of bone-forming cells. Treatment of osteoporosis, osteoarthritis, bone degenerative disorders, or periodontal disease, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes may also be possible using the composition of the invention.

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Another category of tissue regeneration activity that may involve the polypeptide of the present invention is tendon/ligament formation. Induction of tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the 15 . treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The compositions of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a composition may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a composition of the invention.

Compositions of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

Compositions of the present invention may also be involved in the generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine,

kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring may allow normal tissue to regenerate. A polypeptide of the present invention may also exhibit angiogenic activity.

A composition of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A composition of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Therapeutic compositions of the invention can be used in the following:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H. I. and Rovee, D. T., eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

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# 4.10.7 IMMUNE STIMULATING OR SUPPRESSING ACTIVITY

A polypeptide of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A polynucleotide of the invention can encode a polypeptide exhibiting such activities. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpes viruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, proteins of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

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Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein (or antagonists thereof, including antibodies) of the present invention may also to be useful in the treatment of allergic reactions and conditions (e.g., anaphylaxis, serum sickness, drug reactions, food allergies, insect venom allergies, mastocytosis, allergic rhinitis, hypersensitivity pneumonitis, urticaria, angioedema, eczema, atopic dermatitis, allergic contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, allergic conjunctivitis, atopic keratoconjunctivitis, venereal keratoconjunctivitis, giant papillary conjunctivitis and contact allergies), such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein (or antagonists thereof) of the present invention. The therapeutic effects of the polypeptides or antagonists thereof on allergic reactions can be evaluated by in vivo animals models such as the cumulative contact enhancement test (Lastborn et al., Toxicology 125: 59-66, 1998), skin prick test (Hoffmann et al., Allergy 54: 446-54, 1999), guinea pig skin sensitization test (Vohr et al., Arch. Toxocol. 73: 501-9), and murine local lymph node assay (Kimber et al., J. Toxicol. Environ. Health 53: 563-79).

Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue

transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a therapeutic composition of the invention may prevent cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, a lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular therapeutic compositions in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of therapeutic compositions of the invention on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block stimulation of T cells can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (e.g., a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial

immune response. For example, enhancing an immune response may be useful in cases of viral infection, including systemic viral diseases such as influenza, the common cold, and encephalitis.

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Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

A polypeptide of the present invention may provide the necessary stimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient mounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I alpha chain protein and β₂ microglobulin protein or an MHC class II alpha chain protein and an MHC class II beta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J.

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Immunol. 135:1564-1572, 1985; Takai et al., I. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bowman et al., J. Virology 61:1992-1998; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J. J. and Brunswick, M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al.,

Proc. Nat. Acad Sci. USA 88:7548-7551, 1991. 35

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# 4.10.8 ACTIVIN/INHIBIN ACTIVITY

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A polypeptide of the present invention may also exhibit activin- or inhibin-related activities. A polynucleotide of the invention may encode a polypeptide exhibiting such characteristics. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a polypeptide of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, U.S. Pat. No. 4,798,885. A polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as, but not limited to, cows, sheep and pigs.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods.

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

# 4.10.9 CHEMOTACTIC/CHEMOKINETIC ACTIVITY

A polypeptide of the present invention may be involved in chemotactic or chemokinetic activity for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Chemotactic and chemokinetic receptor activation can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic compositions (e.g. proteins, antibodies, binding partners, or modulators of the invention) provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

Therapeutic compositions of the invention can be used in the following:

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Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Marguiles, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

# 4.10.10 HEMOSTATIC AND THROMBOLYTIC ACTIVITY

A polypeptide of the invention may also be involved in hemostatis or thrombolysis or thrombosis. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Compositions may be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A composition of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

Therapeutic compositions of the invention can be used in the following:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

# 4.10.11 CANCER DIAGNOSIS AND THERAPY

Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of polynucleotides or polypeptides of the

invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention may indicate a hereditary risk of cancer, a precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

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Cancer treatments promote tumor regression by inhibiting tumor cell proliferation, inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Therapeutic compositions of the invention may be effective in adult and pediatric oncology including in solid phase tumors/malignancies, locally advanced tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases, blood cell malignancies including multiple myeloma, acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma, tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Karposi's sarcoma.

Polypeptides, polynucleotides, or modulators of polypeptides of the invention (including inhibitors and stimulators of the biological activity of the polypeptide of the invention) may be administered to treat cancer. Therapeutic compositions can be administered in therapeutically effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the polypeptide or modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. The use of anti-cancer cocktails as a cancer treatment is routine.

Anti-cancer drugs that are well known in the art and can be used as a treatment in combination with the polypeptide or modulator of the invention include: Actinomycin D, Aminoglutethimide, Asparaginase, Bleomycin, Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cisDDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin,
Daunorubicin HCl, Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide acetate (LHRH-releasing factor analog), Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine, Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl,
Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these individuals with therapeutically effective doses of the polypeptide of the invention to reduce the risk of developing cancers.

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In vitro models can be used to determine the effective doses of the polypeptide of the invention as a potential cancer treatment. These in vitro models include proliferation assays of cultured tumor cells, growth of cultured tumor cells in soft agar (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wily-Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999), respectively. Suitable tumor cells lines are available, e.g. from American Type Tissue Culture Collection catalogs.

## 4.10.12 RECEPTOR/LIGAND ACTIVITY

A polypeptide of the present invention may also demonstrate activity as receptor, receptor ligand or inhibitor or agonist of receptor/ligand interactions. A polynucleotide of the invention can encode a polypeptide exhibiting such characteristics. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions

and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley- Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1- 7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

By way of example, the polypeptides of the invention may be used as a receptor for a ligand(s) thereby transmitting the biological activity of that ligand(s). Ligands may be identified through binding assays, affinity chromatography, dihybrid screening assays, BIAcore assays, gel overlay assays, or other methods known in the art.

Studies characterizing drugs or proteins as agonist or antagonist or partial agonists or a partial antagonist require the use of other proteins as competing ligands. The polypeptides of the present invention or ligand(s) thereof may be labeled by being coupled to radioisotopes, colorimetric molecules or a toxin molecules by conventional methods. ("Guide to Protein Purification" Murray P. Deutscher (ed) Methods in Enzymology Vol. 182 (1990) Academic Press, Inc. San Diego). Examples of radioisotopes include, but are not limited to, tritium and carbon-14. Examples of colorimetric molecules include, but are not limited to, fluorescent molecules such as fluorescamine, or rhodamine or other colorimetric molecules. Examples of toxins include, but are not limited, to ricin.

#### 4.10.13 DRUG SCREENING

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This invention is particularly useful for screening chemical compounds by using the novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques. The polypeptides or fragments employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface or located intracellularly. One method of drug screening

utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between polypeptides of the invention or fragments and the agent being tested or examine the diminution in complex formation between the novel polypeptides and an appropriate cell line, which are well known in the art.

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Sources for test compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of polypeptides of the invention include (1) inorganic and organic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms themselves. Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally occurring) variants thereof. For a review, see *Science 282*:63-68 (1998).

Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, Curr. Opin. Biotechnol. 8:701-707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., Mol. Biotechnol, 9(3):205-23 (1998); Hruby et al., Curr Opin Chem Biol, 1(1):114-19 (1997); Dorner et al., Bioorg Med Chem, 4(5):709-15 (1996) (alkylated dipeptides).

Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to bind a polypeptide of the invention. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

The binding molecules thus identified may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells such as radioisotopes. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for a polypeptide of the invention. Alternatively, the binding molecules may be complexed with imaging agents for targeting and imaging purposes.

#### 4.10.14 ASSAY FOR RECEPTOR ACTIVITY

The invention also provides methods to detect specific binding of a polypeptide e.g. a ligand or a receptor. The art provides numerous assays particularly useful for identifying previously unknown binding partners for receptor polypeptides of the invention. For example, expression cloning using mammalian or bacterial cells, or dihybrid screening assays can be used to identify polynucleotides encoding binding partners. As another example, affinity chromatography with the appropriate immobilized polypeptide of the invention can be used to isolate polypeptides that recognize and bind polypeptides of the invention. There are a number of different libraries used for the identification of compounds, and in particular small molecules, that modulate (i.e., increase or decrease) biological activity of a polypeptide of the invention. Ligands for receptor polypeptides of the invention can also be identified by adding exogenous ligands, or cocktails of ligands to two cells populations that are genetically identical except for the expression of the receptor of the invention: one cell population expresses the receptor of the invention whereas the other does not. The response of the two cell populations to the addition of ligands(s) are then compared. Alternatively, an expression library can be co-expressed with the polypeptide of the invention in cells and assayed for an autocrine response to identify potential ligand(s). As still another example, BIAcore assays, gel overlay assays, or other methods known in the art can be used to identify binding partner polypeptides, including, (1) organic and inorganic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

The role of downstream intracellular signaling molecules in the signaling cascade of the polypeptide of the invention can be determined. For example, a chimeric protein in which the cytoplasmic domain of the polypeptide of the invention is fused to the extracellular portion of a protein, whose ligand has been identified, is produced in a host cell. The cell is then incubated with the ligand specific for the extracellular portion of the chimeric protein, thereby activating the chimeric receptor. Known downstream proteins involved in intracellular signaling can then be assayed for expected modifications i.e. phosphorylation. Other methods known to those in the art can also be used to identify signaling molecules involved in receptor activity.

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# 4.10.15 ANTI-INFLAMMATORY ACTIVITY

Compositions of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Compositions with such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation intimation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Compositions of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material. Compositions of this invention may be utilized to prevent or treat conditions such as, but not limited to, sepsis, acute pancreatitis, endotoxin shock, cytokine induced shock, rheumatoid arthritis, chronic inflammatory arthritis, pancreatic cell damage from diabetes mellitus type 1, graft versus host disease, inflammatory bowel disease, inflamation associated with pulmonary disease, other autoimmune disease or inflammatory disease, an antiproliferative agent such as for acute or chronic mylegenous leukemia or in the prevention of premature labor secondary to intrauterine infections.

#### **4.10.16 LEUKEMIAS**

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Leukemias and related disorders may be treated or prevented by administration of a
therapeutic that promotes or inhibits function of the polynucleotides and/or polypeptides of the invention. Such leukemias and related disorders include but are not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia (for a review of such disorders, see
Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia).

#### 4.10.17 NERVOUS SYSTEM DISORDERS

Nervous system disorders, involving cell types which can be tested for efficacy of intervention with compounds that modulate the activity of the polynucleotides and/or polypeptides of the invention, and which can be treated upon thus observing an indication of

therapeutic utility, include but are not limited to nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the invention include but are not limited to the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems:

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- (i) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries;
- (ii) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia;
  - (iii) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis;
  - (iv) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis;
  - (v) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration;
  - (vi) neurological lesions associated with systemic diseases including but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis;
- (vii) lesions caused by toxic substances including alcohol, lead, or particular
   neurotoxins; and
  - (viii) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including but not limited to multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

Therapeutics which are useful according to the invention for treatment of a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, therapeutics which elicit any of the following effects may be useful according to the invention:

(i) increased survival time of neurons in culture;

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- (ii) increased sprouting of neurons in culture or in vivo;
- (iii) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or
  - (iv) decreased symptoms of neuron dysfunction in vivo.

Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may be measured by the method set forth in Arakawa et al. (1990, J. Neurosci. 10:3507-3515); increased sprouting of neurons may be detected by methods set forth in Pestronk et al. (1980, Exp. Neurol. 70:65-82) or Brown et al. (1981, Ann. Rev. Neurosci. 4:17-42); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include but are not limited to disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including but not limited to progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

#### 4.10.18 OTHER ACTIVITIES

A polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape);

effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, co-factors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

# 4.10.19 IDENTIFICATION OF POLYMORPHISMS

The demonstration of polymorphisms makes possible the identification of such polymorphisms in human subjects and the pharmacogenetic use of this information for diagnosis and treatment. Such polymorphisms may be associated with, e.g., differential predisposition or susceptibility to various disease states (such as disorders involving inflammation or immune response) or a differential response to drug administration, and this genetic information can be used to tailor preventive or therapeutic treatment appropriately. For example, the existence of a polymorphism associated with a predisposition to inflammation or autoimmune disease makes possible the diagnosis of this condition in humans by identifying the presence of the polymorphism.

Polymorphisms can be identified in a variety of ways known in the art which all generally involve obtaining a sample from a patient, analyzing DNA from the sample, optionally involving isolation or amplification of the DNA, and identifying the presence of the polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment of genomic DNA which may then be sequenced. Alternatively, the DNA may be subjected to allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides are hybridized to the DNA under conditions permitting detection of a single base mismatch) or to a single nucleotide extension assay (in which an oligonucleotide that hybridizes immediately adjacent to the position of the polymorphism is extended with one or more labeled nucleotides). In addition, traditional restriction fragment length polymorphism analysis (using restriction enzymes that provide differential digestion of the genomic DNA depending on the presence or

absence of the polymorphism) may be performed. Arrays with nucleotide sequences of the present invention can be used to detect polymorphisms. The array can comprise modified nucleotide sequences of the present invention in order to detect the nucleotide sequences of the present invention. In the alternative, any one of the nucleotide sequences of the present invention can be placed on the array to detect changes from those sequences.

Alternatively a polymorphism resulting in a change in the amino acid sequence could also be detected by detecting a corresponding change in amino acid sequence of the protein, e.g., by an antibody specific to the variant sequence.

## 4.10.20 ARTHRITIS AND INFLAMMATION

The immunosuppressive effects of the compositions of the invention against rheumatoid arthritis is determined in an experimental animal model system. The experimental model system is adjuvant induced arthritis in rats, and the protocol is described by J. Holoshitz, et at., 1983, Science, 219:56, or by B. Waksman et al., 1963, Int. Arch. Allergy Appl. Immunol., 23:129. Induction of the disease can be caused by a single injection, generally intradermally, of a suspension of killed Mycobacterium tuberculosis in complete Freund's adjuvant (CFA). The route of injection can vary, but rats may be injected at the base of the tail with an adjuvant mixture. The polypeptide is administered in phosphate buffered solution (PBS) at a dose of about 1-5 mg/kg. The control consists of administering PBS only.

The procedure for testing the effects of the test compound would consist of intradermally injecting killed Mycobacterium tuberculosis in CFA followed by immediately administering the test compound and subsequent treatment every other day until day 24. At 14, 15, 18, 20, 22, and 24 days after injection of Mycobacterium CFA, an overall arthritis score may be obtained as described by J. Holoskitz above. An analysis of the data would reveal that the test compound would have a dramatic affect on the swelling of the joints as measured by a decrease of the arthritis score.

#### 4.11 THERAPEUTIC METHODS

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The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including antisense polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are not limited to, those exemplified herein.

#### 4.11.1 **EXAMPLE**

One embodiment of the invention is the administration of an effective amount of the polypeptides or other composition of the invention to individuals affected by a disease or disorder that can be modulated by regulating the peptides of the invention. While the mode of administration is not particularly important, parenteral administration is preferred. An exemplary mode of administration is to deliver an intravenous bolus. The dosage of the polypeptides or other composition of the invention will normally be determined by the prescribing physician. It is to be expected that the dosage will vary according to the age, weight, condition and response of the individual patient. Typically, the amount of polypeptide administered per dose will be in the range of about 0.01µg/kg to 100 mg/kg of body weight, with the preferred dose being about 0.1µg/kg to 10 mg/kg of patient body weight. For parenteral administration, polypeptides of the invention will be formulated in an injectable form combined with a pharmaceutically acceptable parenteral vehicle. Such vehicles are well known in the art and examples include water, saline, Ringer's solution, dextrose solution, and solutions consisting of small amounts of the human serum albumin. The vehicle may contain minor amounts of additives that maintain the isotonicity and stability of the polypeptide or other active ingredient. The preparation of such solutions is within the skill of the art.

# 4.12 PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION

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A protein or other composition of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources and including antibodies and other binding partners of the polypeptides of the invention) may be administered to a patient in need, by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a variety of disorders. Such a composition may optionally contain (in addition to protein or other active ingredient and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the disease or disorder in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet-derived growth

factor (PDGF), transforming growth factors (TGF- $\alpha$  and TGF- $\beta$ ), insulin-like growth factor (IGF), as well as cytokines described herein.

The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or other active ingredient or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein or other active ingredient of the invention, or to minimize side effects. Conversely, protein or other active ingredient of the present invention may be included in formulations of the particular clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent (such as IL-1Ra, IL-1 Hy1, IL-1 Hy2, anti-TNF, corticosteroids, immunosuppressive agents). A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

As an alternative to being included in a pharmaceutical composition of the invention including a first protein, a second protein or a therapeutic agent may be concurrently administered with the first protein (e.g., at the same time, or at differing times provided that therapeutic concentrations of the combination of agents is achieved at the treatment site). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms, e.g., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein or other active ingredient of the present invention is administered to a mammal having a condition to be treated. Protein or other active ingredient of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co- administered with one or more cytokines, lymphokines or other

hematopoietic factors, protein or other active ingredient of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein or other active ingredient of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

# 4.12.1 ROUTES OF ADMINISTRATION

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Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Administration of protein or other active ingredient of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a arthritic joints or in fibrotic tissue, often in a depot or sustained release formulation. In order to prevent the scarring process frequently occurring as complication of glaucoma surgery, the compounds may be administered topically, for example, as eye drops. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a specific antibody, targeting, for example, arthritic or fibrotic tissue. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

The polypeptides of the invention are administered by any route that delivers an effective dosage to the desired site of action. The determination of a suitable route of administration and an effective dosage for a particular indication is within the level of skill in the art. Preferably for wound treatment, one administers the therapeutic compound directly to the site. Suitable dosage ranges for the polypeptides of the invention can be extrapolated from these dosages or from similar studies in appropriate animal models. Dosages can then be adjusted as necessary by the clinician to provide maximal therapeutic benefit.

# 4.12.2 COMPOSITIONS/FORMULATIONS

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers

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comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of protein or other active ingredient of the present invention is administered orally, protein or other active ingredient of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein or other active ingredient of the present invention, and preferably from about 25 to 90% protein or other active ingredient of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein or other active ingredient of the present invention, and preferably from about 1 to 50% protein or other active ingredient of the present invention.

When a therapeutically effective amount of protein or other active ingredient of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein or other active ingredient of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein or other active ingredient solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein or other active ingredient of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

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For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, tale, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. The compounds may be formulated for parenteral

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administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a co-solvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other

sugars or polysaccharides may substitute for dextrose. Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein or other active ingredient stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Many of the active ingredients of the invention may be provided as salts with pharmaceutically compatible counter ions. Such pharmaceutically acceptable base addition salts are those salts which retain the biological effectiveness and properties of the free acids and which are obtained by reaction with inorganic or organic bases such as sodium hydroxide, magnesium hydroxide, ammonia, trialkylamine, dialkylamine, monoalkylamine, dibasic amino acids, sodium acetate, potassium benzoate, triethanol amine and the like.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) or other active ingredient(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically

acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithins, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent Nos. 4,235,871; 4,501,728; 4,837,028; and 4,737,323, all of which are incorporated herein by reference.

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The amount of protein or other active ingredient of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein or other active ingredient of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein or other active ingredient of the present invention and observe the patient's response. Larger doses of protein or other active ingredient of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1 µg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein or other active ingredient of the present invention per kg body weight. For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein or other active ingredient of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing or other active ingredient-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

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The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability. Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells. In further compositions, proteins or other active ingredients of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired

patients for such treatment with proteins or other active ingredients of the present invention. The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either in vivo or ex vivo into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA). Cells may also be cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes.

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#### 4.12.3 EFFECTIVE DOSAGE

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from appropriate in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that can be used to more accurately determine useful doses in humans. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC<sub>50</sub> as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the protein's biological activity). Such information can be used to more accurately determine useful doses in humans.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD<sub>50</sub> and ED<sub>50</sub>. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the  $ED_{50}$  with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, e.g., Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the desired effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

An exemplary dosage regimen for polypeptides or other compositions of the invention will be in the range of about 0.01  $\mu$ g/kg to 100 mg/kg of body weight daily, with the preferred dose being about 0.1  $\mu$ g/kg to 25 mg/kg of patient body weight daily, varying in adults and children. Dosing may be once daily, or equivalent doses may be delivered at longer or shorter intervals.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's age and weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

#### 4.12.4 PACKAGING

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The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

#### 4.13 ANTIBODIES

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Also included in the invention are antibodies to proteins, or fragments of proteins of the invention. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain,  $F_{ab}$ ,  $F_{ab}$  and  $F_{(ab)2}$  fragments, and an  $F_{ab}$  expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as  $IgG_1$ ,  $IgG_2$ , and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein, such as an amino acid sequence shown in SEQ ID NO: 237, and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of -related protein that is located on the surface of the protein, e.g., a hydrophilic region. A hydrophobicity analysis of the human related protein sequence will

indicate which regions of a related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, e.g., Hopp and Woods, 1981, Proc. Nat. Acad. Sci. USA 78: 3824-3828; Kyte and Doolittle 1982, J. Mol. Biol. 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

### 5.13.1 Polyclonal Antibodies

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For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

#### 10 5.13.2 Monoclonal Antibodies

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The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro. The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal. The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for

example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

#### 5.13.2 Humanized Antibodies

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The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigenbinding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)).

#### 5.13.3 Human Antibodies

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein.

Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (Bio/Technology 10, 779-783 (1992)); Lonberg et al. (Nature 368 856-859 (1994)); Morrison (Nature 368, 812-13 (1994)); Fishwild et al., (Nature Biotechnology 14, 845-51 (1996)); Neuberger (Nature Biotechnology 14, 826 (1996)); and Lonberg and Huszar (Intern. Rev. Immunol. 13 65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the Xenomouse<sup>TM</sup> as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the

immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

# 5.13.4 Fab Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of  $F_{ab}$  expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal  $F_{ab}$  fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an  $F_{(ab)/2}$  fragment produced by pepsin digestion of an antibody molecule; (ii) an  $F_{ab}$  fragment generated by reducing the disulfide bridges of an  $F_{(ab)/2}$  fragment; (iii) an  $F_{ab}$  fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv)  $F_v$  fragments.

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Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., <u>Science</u> 229:81 (1985) describe a procedure

wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V<sub>H</sub> and V<sub>L</sub> domains of one fragment are forced to pair with the complementary V<sub>L</sub> and V<sub>H</sub> domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., <u>J. Immunol.</u> 147:60 (1991). Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on

a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

### 5.13.6 Heteroconjugate Antibodies

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Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

### 5.13.7 Effector Function Engineering

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced antitumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

### 5.13.8 Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of

bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include <sup>212</sup>Bi, <sup>131</sup>I, <sup>131</sup>In, <sup>90</sup>Y, and <sup>186</sup>Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

#### 4.14 COMPUTER READABLE SEQUENCES

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In one application of this embodiment, a nucleotide sequence of the present invention can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled

artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon a nucleotide sequence of the present invention. As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the nucleotide sequence information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (e.g. text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing any of the nucleotide sequences SEQ ID NO:1-236 and 473-708 or a representative fragment thereof; or a nucleotide sequence at least 95% identical to any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708 in computer readable form, a skilled artisan can routinely access the sequence information for a variety of purposes. Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium. The examples which follow demonstrate how software which implements the BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et al., Comp. Chem. 17:203-207 (1993)) search algorithms on a Sybase system is used to identify open reading frames (ORFs) within a nucleic acid sequence. Such ORFs may be protein encoding fragments and may be useful in producing commercially important proteins such as enzymes used in fermentation reactions and in the production of commercially useful metabolites.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. As stated above, the

computer-based systems of the present invention comprise a data storage means having stored therein a nucleotide sequence of the present invention and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store nucleotide sequence information of the present invention, or a memory access means which can access manufactures having recorded thereon the nucleotide sequence information of the present invention.

As used herein, "search means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of a known sequence which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. Examples of such software includes, but is not limited to, Smith-Waterman, MacPattern (EMBL), BLASTN and BLASTA (NPOLYPEPTIDEIA). A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting homology searches can be adapted for use in the present computer-based systems. As used herein, a "target sequence" can be any nucleic acid or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. The most preferred sequence length of a target sequence is from about 10 to 300 amino acids, more preferably from about 30 to 100 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures and inducible expression elements (protein binding sequences).

#### 4.15 TRIPLE HELIX FORMATION

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In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA or RNA, both of which

methods are based on the binding of a polynucleotide sequence to DNA or RNA.

Polynucleotides suitable for use in these methods are preferably 20 to 40 bases in length and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Olmno, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide.

### 4.16 DIAGNOSTIC ASSAYS AND KITS

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The present invention further provides methods to identify the presence or expression of one of the ORFs of the present invention, or homolog thereof, in a test sample, using a nucleic acid probe or antibodies of the present invention, optionally conjugated or otherwise associated with a suitable label.

In general, methods for detecting a polynucleotide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polynucleotide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polynucleotide of the invention is detected in the sample. Such methods can also comprise contacting a sample under stringent hybridization conditions with nucleic acid primers that anneal to a polynucleotide of the invention under such conditions, and amplifying annealed polynucleotides, so that if a polynucleotide is amplified, a polynucleotide of the invention is detected in the sample.

In general, methods for detecting a polypeptide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polypeptide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polypeptide of the invention is detected in the sample.

In detail, such methods comprise incubating a test sample with one or more of the antibodies or one or more of the nucleic acid probes of the present invention and assaying for binding of the nucleic acid probes or antibodies to components within the test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary.

Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One

skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

### 4.17 MEDICAL IMAGING

The novel polypeptides and binding partners of the invention are useful in medical imaging of sites expressing the molecules of the invention (e.g., where the polypeptide of the invention is involved in the immune response, for imaging sites of inflammation or infection). See, e.g., Kunkel et al., U.S. Pat. NO. 5,413,778. Such methods involve chemical attachment of a labeling or imaging agent, administration of the labeled polypeptide to a subject in a pharmaceutically acceptable carrier, and imaging the labeled polypeptide *in vivo* at the target site.

### 10 4.18 SCREENING ASSAYS

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Using the isolated proteins and polynucleotides of the invention, the present invention further provides methods of obtaining and identifying agents which bind to a polypeptide encoded by an ORF corresponding to any of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708, or bind to a specific domain of the polypeptide encoded by the nucleic acid. In detail, said method comprises the steps of:

- (a) contacting an agent with an isolated protein encoded by an ORF of the present invention, or nucleic acid of the invention; and
  - (b) determining whether the agent binds to said protein or said nucleic acid.

In general, therefore, such methods for identifying compounds that bind to a polynucleotide of the invention can comprise contacting a compound with a polynucleotide of the invention for a time sufficient to form a polynucleotide/compound complex, and detecting the complex, so that if a polynucleotide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Likewise, in general, therefore, such methods for identifying compounds that bind to a polypeptide of the invention can comprise contacting a compound with a polypeptide of the invention for a time sufficient to form a polypeptide/compound complex, and detecting the complex, so that if a polypeptide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Methods for identifying compounds that bind to a polypeptide of the invention can also comprise contacting a compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a receptor gene sequence in the cell, and detecting the complex by detecting reporter gene sequence expression, so that if a polypeptide/compound complex is detected, a compound that binds a polypeptide of the invention is identified.

Compounds identified via such methods can include compounds which modulate the activity of a polypeptide of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds which modulate the expression of a polynucleotide of the invention (that is, increase or decrease expression relative to expression levels observed in the absence of the compound). Compounds, such as compounds identified via the methods of the invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

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The agents screened in the above assay can be, but are not limited to, peptides, carbohydrates, vitamin derivatives, or other pharmaceutical agents. The agents can be selected and screened at random or rationally selected or designed using protein modeling techniques.

For random screening, agents such as peptides, carbohydrates, pharmaceutical agents and the like are selected at random and are assayed for their ability to bind to the protein encoded by the ORF of the present invention. Alternatively, agents may be rationally selected or designed. As used herein, an agent is said to be "rationally selected or designed" when the agent is chosen based on the configuration of the particular protein. For example, one skilled in the art can readily adapt currently available procedures to generate peptides, pharmaceutical agents and the like, capable of binding to a specific peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: Antisense Peptides," In Synthetic Peptides, A User's Guide, W.H. Freeman, NY (1992), pp. 289-307, and Kaspczak et al., Biochemistry 28:9230-8 (1989), or pharmaceutical agents, or the like.

In addition to the foregoing, one class of agents of the present invention, as broadly described, can be used to control gene expression through binding to one of the ORFs or EMFs of the present invention. As described above, such agents can be randomly screened or rationally designed/selected. Targeting the ORF or EMF allows a skilled artisan to design sequence specific or element specific agents, modulating the expression of either a single ORF or multiple ORFs which rely on the same EMF for expression control. One class of DNA binding agents are agents which contain base residues which hybridize or form a triple helix formation by binding to DNA or RNA. Such agents can be based on the classic phosphodiester, ribonucleic acid backbone, or can be a variety of sulfhydryl or polymeric derivatives which have base attachment capacity.

Agents suitable for use in these methods preferably contain 20 to 40 bases and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560

(1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide and other DNA binding agents.

Agents which bind to a protein encoded by one of the ORFs of the present invention can be used as a diagnostic agent. Agents which bind to a protein encoded by one of the ORFs of the present invention can be formulated using known techniques to generate a pharmaceutical composition.

### 4.19 USE OF NUCLEIC ACIDS AS PROBES

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Another aspect of the subject invention is to provide for polypeptide-specific nucleic acid hybridization probes capable of hybridizing with naturally occurring nucleotide sequences. The hybridization probes of the subject invention may be derived from any of the nucleotide sequences SEQ ID NO:1-236 and 473-708. Because the corresponding gene is only expressed in a limited number of tissues, a hybridization probe derived from of any of the nucleotide sequences SEQ ID NO:1-236 and 473-708 can be used as an indicator of the presence of RNA of cell type of such a tissue in a sample.

Any suitable hybridization technique can be employed, such as, for example, in situ hybridization. PCR as described in US Patents Nos. 4,683,195 and 4,965,188 provides additional uses for oligonucleotides based upon the nucleotide sequences. Such probes used in PCR may be of recombinant origin, may be chemically synthesized, or a mixture of both. The probe will comprise a discrete nucleotide sequence for the detection of identical sequences or a degenerate pool of possible sequences for identification of closely related genomic sequences.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA polymerase and the appropriate radioactively labeled nucleotides. The nucleotide sequences may be used to construct hybridization probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well known genetic and/or chromosomal mapping techniques. These techniques include in situ hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to

known chromosomes, and the like. The technique of fluorescent in situ hybridization of chromosome spreads has been described, among other places, in Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York NY.

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Fluorescent in situ hybridization of chromosomal preparations and other physical chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found in the 1994 Genome Issue of Science (265:1981f). Correlation between the location of a nucleic acid on a physical chromosomal map and a specific disease (or predisposition to a specific disease) may help delimit the region of DNA associated with that genetic disease. The nucleotide sequences of the subject invention may be used to detect differences in gene sequences between normal, carrier or affected individuals.

# 4.20 PREPARATION OF SUPPORT BOUND OLIGONUCLEOTIDES

Oligonucleotides, i.e., small nucleic acid segments, may be readily prepared by, for example, directly synthesizing the oligonucleotide by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer.

Support bound oligonucleotides may be prepared by any of the methods known to those of skill in the art using any suitable support such as glass, polystyrene or Teflon. One strategy is to precisely spot oligonucleotides synthesized by standard synthesizers. Immobilization can be achieved using passive adsorption (Inouye & Hondo, (1990) J. Clin. Microbiol. 28(6) 1469-72); using UV light (Nagata et al., 1985; Dahlen et al., 1987; Morrissey & Collins, (1989) Mol. Cell Probes 3(2) 189-207) or by covalent binding of base modified DNA (Keller et al., 1988; 1989); all references being specifically incorporated herein.

Another strategy that may be employed is the use of the strong biotin-streptavidin interaction as a linker. For example, Broude *et al.* (1994) Proc. Natl. Acad. Sci. USA 91(8) 3072-6, describe the use of biotinylated probes, although these are duplex probes, that are immobilized on streptavidin-coated magnetic beads. Streptavidin-coated beads may be purchased from Dynal, Oslo. Of course, this same linking chemistry is applicable to coating any surface with streptavidin. Biotinylated probes may be purchased from various sources, such as, e.g., Operon Technologies (Alameda, CA).

Nunc Laboratories (Naperville, IL) is also selling suitable material that could be used. Nunc Laboratories have developed a method by which DNA can be covalently bound to the microwell surface termed Covalink NH. CovaLink NH is a polystyrene surface grafted with secondary amino groups (>NH) that serve as bridge-heads for further covalent coupling. CovaLink Modules may be purchased from Nunc Laboratories. DNA molecules may be bound to CovaLink exclusively at the

5'-end by a phosphoramidate bond, allowing immobilization of more than 1 pmol of DNA (Rasmussen et al., (1991) Anal. Biochem. 198(1) 138-42).

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The use of CovaLink NH strips for covalent binding of DNA molecules at the 5'-end has been described (Rasmussen et al., (1991). In this technology, a phosphoramidate bond is employed (Chu et al., (1983) Nucleic Acids Res. 11(8) 6513-29). This is beneficial as immobilization using only a single covalent bond is preferred. The phosphoramidate bond joins the DNA to the CovaLink NH secondary amino groups that are positioned at the end of spacer arms covalently grafted onto the polystyrene surface through a 2 nm long spacer arm. To link an oligonucleotide to CovaLink NH via an phosphoramidate bond, the oligonucleotide terminus must have a 5'-end phosphate group. It is, perhaps, even possible for biotin to be covalently bound to CovaLink and then streptavidin used to bind the probes.

More specifically, the linkage method includes dissolving DNA in water (7.5 ng/ul) and denaturing for 10 min. at 95°C and cooling on ice for 10 min. Ice-cold 0.1 M 1-methylimidazole, pH 7.0 (1-MeIm<sub>7</sub>), is then added to a final concentration of 10 mM 1-MeIm<sub>7</sub>. A ss DNA solution is then dispensed into CovaLink NH strips (75 ul/well) standing on ice.

Carbodiimide 0.2 M 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), dissolved in 10 mM 1-MeIm<sub>7</sub>, is made fresh and 25 ul added per well. The strips are incubated for 5 hours at 50°C. After incubation the strips are washed using, e.g., Nunc-Immuno Wash; first the wells are washed 3 times, then they are soaked with washing solution for 5 min., and finally they are washed 3 times (where in the washing solution is 0.4 N NaOH, 0.25% SDS heated to 50°C).

It is contemplated that a further suitable method for use with the present invention is that described in PCT Patent Application WO 90/03382 (Southern & Maskos), incorporated herein by reference. This method of preparing an oligonucleotide bound to a support involves attaching a nucleoside 3'-reagent through the phosphate group by a covalent phosphodiester link to aliphatic hydroxyl groups carried by the support. The oligonucleotide is then synthesized on the supported nucleoside and protecting groups removed from the synthetic oligonucleotide chain under standard conditions that do not cleave the oligonucleotide from the support. Suitable reagents include nucleoside phosphoramidite and nucleoside hydrogen phosphorate.

An on-chip strategy for the preparation of DNA probe for the preparation of DNA probe arrays may be employed. For example, addressable laser-activated photodeprotection may be employed in the chemical synthesis of oligonucleotides directly on a glass surface, as described by Fodor *et al.* (1991) Science 251(4995) 767-73, incorporated herein by reference. Probes may also be immobilized on nylon supports as described by Van Ness *et al.* (1991) Nucleic Acids Res. 19(12) 3345-50; or linked to Teflon using the method of Duncan & Cavalier (1988) Anal. Biochem. 169(1) 104-8; all references being specifically incorporated herein.

To link an oligonucleotide to a nylon support, as described by Van Ness *et al.* (1991), requires activation of the nylon surface via alkylation and selective activation of the 5'-amine of oligonucleotides with cyanuric chloride.

One particular way to prepare support bound oligonucleotides is to utilize the light-generated synthesis described by Pease *et al.*, (1994) PNAS USA 91(11) 5022-6, incorporated herein by reference). These authors used current photolithographic techniques to generate arrays of immobilized oligonucleotide probes (DNA chips). These methods, in which light is used to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays, utilize photolabile 5'-protected *N*-acyl-deoxynucleoside phosphoramidites, surface linker chemistry and versatile combinatorial synthesis strategies. A matrix of 256 spatially defined oligonucleotide probes may be generated in this manner.

# 4.21 PREPARATION OF NUCLEIC ACID FRAGMENTS

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The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or YAC inserts, and RNA, including mRNA without any amplification steps. For example, Sambrook *et al.* (1989) describes three protocols for the isolation of high molecular weight DNA from mammalian cells (p. 9.14-9.23).

DNA fragments may be prepared as clones in M13, plasmid or lambda vectors and/or prepared directly from genomic DNA or cDNA by PCR or other amplification methods. Samples may be prepared or dispensed in multiwell plates. About 100-1000 ng of DNA samples may be prepared in 2-500 ml of final volume.

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described at 9.24-9.28 of Sambrook et al. (1989), shearing by ultrasound and NaOH treatment.

Low pressure shearing is also appropriate, as described by Schriefer et al. (1990) Nucleic Acids Res. 18(24) 7455-6, incorporated herein by reference). In this method, DNA samples are passed through a small French pressure cell at a variety of low to intermediate pressures. A lever device allows controlled application of low to intermediate pressures to the cell. The results of these studies indicate that low-pressure shearing is a useful alternative to sonic and enzymatic DNA fragmentation methods.

One particularly suitable way for fragmenting DNA is contemplated to be that using the two base recognition endonuclease, CviJI, described by Fitzgerald et al. (1992) Nucleic Acids Res. 20(14) 3753-62. These authors described an approach for the rapid fragmentation and fractionation

of DNA into particular sizes that they contemplated to be suitable for shotgun cloning and sequencing.

The restriction endonuclease CviJI normally cleaves the recognition sequence PuGCPy between the G and C to leave blunt ends. Atypical reaction conditions, which alter the specificity of this enzyme (CviJI\*\*), yield a quasi-random distribution of DNA fragments form the small molecule pUC19 (2688 base pairs). Fitzgerald et al. (1992) quantitatively evaluated the randomness of this fragmentation strategy, using a CviJI\*\* digest of pUC19 that was size fractionated by a rapid gel filtration method and directly ligated, without end repair, to a lac Z minus M13 cloning vector. Sequence analysis of 76 clones showed that CviJI\*\* restricts pyGCPy and PuGCPu, in addition to PuGCPy sites, and that new sequence data is accumulated at a rate consistent with random fragmentation.

As reported in the literature, advantages of this approach compared to sonication and agarose gel fractionation include: smaller amounts of DNA are required (0.2-0.5 ug instead of 2-5 ug); and fewer steps are involved (no preligation, end repair, chemical extraction, or agarose gel electrophoresis and elution are needed

Irrespective of the manner in which the nucleic acid fragments are obtained or prepared, it is important to denature the DNA to give single stranded pieces available for hybridization. This is achieved by incubating the DNA solution for 2-5 minutes at 80-90°C. The solution is then cooled quickly to 2°C to prevent renaturation of the DNA fragments before they are contacted with the chip. Phosphate groups must also be removed from genomic DNA by methods known in the art.

#### 4.22 PREPARATION OF DNA ARRAYS

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Arrays may be prepared by spotting DNA samples on a support such as a nylon membrane. Spotting may be performed by using arrays of metal pins (the positions of which correspond to an array of wells in a microtiter plate) to repeated by transfer of about 20 nl of a DNA solution to a nylon membrane. By offset printing, a density of dots higher than the density of the wells is achieved. One to 25 dots may be accommodated in 1 mm², depending on the type of label used. By avoiding spotting in some preselected number of rows and columns, separate subsets (subarrays) may be formed. Samples in one subarray may be the same genomic segment of DNA (or the same gene) from different individuals, or may be different, overlapped genomic clones. Each of the subarrays may represent replica spotting of the same samples. In one example, a selected gene segment may be amplified from 64 patients. For each patient, the amplified gene segment may be in one 96-well plate (all 96 wells containing the same sample). A plate for each of the 64 patients is prepared. By using a 96-pin device, all samples may be spotted on one 8 x 12 cm membrane.

Subarrays may contain 64 samples, one from each patient. Where the 96 subarrays are identical, the dot span may be 1 mm<sup>2</sup> and there may be a 1 mm space between subarrays.

Another approach is to use membranes or plates (available from NUNC, Naperville, Illinois) which may be partitioned by physical spacers e.g. a plastic grid molded over the membrane, the grid being similar to the sort of membrane applied to the bottom of multiwell plates, or hydrophobic strips. A fixed physical spacer is not preferred for imaging by exposure to flat phosphor-storage screens or x-ray films.

The present invention is illustrated in the following examples. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention. Accordingly, it is intended that the broader aspects of the present invention not be limited to the disclosure of the following examples. The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and compositions and methods which are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations which should be placed upon the scope of the invention are those which appear in the appended claims.

All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

#### 5.0 EXAMPLES

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#### **5.1.1 EXAMPLE 1**

### Novel Nucleic Acid Sequences Obtained From Various Libraries

A plurality of novel nucleic acids were obtained from cDNA libraries prepared from various human tissues and in some cases isolated from a genomic library derived from human chromosome using standard PCR, SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using primers specific for the vector sequences which flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (e.g., 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones were selected for sequencing.

In some cases, the 5' sequence of the amplified inserts was then deduced using a typical Sanger sequencing protocol. PCR products were purified and subjected to fluorescent dye terminator cycle sequencing. Single pass gel sequencing was done using a 377 Applied Biosystems

(ABI) sequencer to obtain the novel nucleic acid sequences. In some cases RACE (Random Amplification of cDNA Ends) was performed to further extend the sequence in the 5' direction.

### 5.1.2 EXAMPLE 2

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## **Assemblage of Novel Nucleic Acids**

The contigs or nucleic acids of the present invention, designated as SEQ ID NO: 473-708 were assembled using an EST sequence as a seed. Then a recursive algorithm was used to extend the seed EST into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 114, gb pri 114, and UniGene version 101) that belong to this assemblage. The algorithm terminated when there was no additional sequences from the above databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

A polypeptide was predicted to be encoded by each of SEQ ID NO:473-708 as set forth below. The polypeptides was predicted using a software program called FASTY (available from <a href="http://fasta.bioch.virginia.edu">http://fasta.bioch.virginia.edu</a>) which selects a polypeptides based on a comparison of translated novel polynucleotide to known polynucleotides (W.R. Pearson, Methods in Enzymology, 183:63-98 (1990), herein incorporated by reference. The predicted polypeptides are shown in Table 7.

#### **5.2.2 EXAMPLE 3**

#### **Novel Nucleic Acids**

Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e. dbEST version 117, gb pri 117, UniGene version 117, Genpept release 117). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, edext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS:1-217.

Table 1 shows the various tissue sources of SEQ ID NO: 1-217.

The nearest neighbor results for SEQ ID NO: 1-217 were obtained by a BLASTP version 2.0al 19MP-WashU search against Genpept release 120 and Geneseq October 12, 2000 release 21 (Derwent), using BLAST algorithm. The nearest neighbor result showed the closest homologue for SEQ ID NO: 1-217 from Genpept. The translated amino acid sequences for which the nucleic acid sequence encodes are shown in the Sequence Listing. The homologs with identifiable functions for SEQ ID NO: 1-217 are shown in Table 2 below.

Using eMatrix software package (Stanford University, Stanford, CA) (Wu et al., J. Comp. Biol., Vol. 6 pp. 219-235 (1999) herein incorporated by reference), all the sequences were examined to determine whether they had identifiable signature regions. Table 3 shows the signature region found in the indicated polypeptide sequences, the description of the signature, the eMatrix p-value(s) and the position(s) of the signature within the polypeptide sequence.

Using the pFam software program (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1) pp. 320-322 (1998) herein incorporated by reference) all the polypeptide sequences were examined for domains with homology to certain peptide domains. Table 4 shows the name of the domain found, the description, the p-value and the pFam score for the identified domain within the sequence.

The nucleotide sequence within the sequences that codes for signal peptide sequences and their cleavage sites can be determine from using Neural Network SignalP V1.1 program (from Center for Biological Sequence Analysis, The Technical University of Denmark). The process for identifying prokaryotic and eukaryotic signal peptides and their cleavage sites are also disclosed by Henrik Nielson, Jacob Engelbrecht, Soren Brunak, and Gunnar von Heijne in the publication "Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites" Protein Engineering, Vol. 10, no. 1, pp. 1-6 (1997), incorporated herein by reference. A maximum S score and a mean S score, as described in the Nielson et as reference, was obtained for the polypeptide sequences. Table 5 shows the position of the signal peptide in each of the polypeptides and the maximum score and mean score associated with that signal peptide.

### 5.3.2 EXAMPLE 4

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### **Novel Nucleic Acids**

Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e., dbEST version 118, gb pri 118, UniGene version 118, Genpept release 118). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, edext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS: 218-236.

Table 1 shows the various tissue sources of SEQ ID NO: 218-236.

The homology results for SEQ ID NO: 218-236 were obtained by a BLASTP version 2.0al 19MP-WashU search against Genpept release 120 and Geneseq October 12, 2000 release

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21 (Derwent), using BLAST algorithm. The nearest neighbor result showed the homologs for SEQ ID NO: 218-236 from Genpept. The translated amino acid sequences for which the nucleic acid sequence encodes are shown in the Sequence Listing. The homologues with identifiable functions for SEQ ID NO: 218-236 are shown in Table 2 below.

Using eMatrix software package (Stanford University, Stanford, CA) (Wu et al., J. Comp. Biol., Vol. 6 pp. 219-235 (1999) herein incorporated by reference), all the sequences were examined to determine whether they had identifiable signature regions. Table 3 shows the signature region found in the indicated polypeptide sequences, the description of the signature, the eMatrix p-value(s) and the position(s) of the signature within the polypeptide sequence.

Using the pFam software program (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1) pp. 320-322 (1998) herein incorporated by reference) all the polypeptide sequences were examined for domains with homology to certain peptide domains. Table 4 shows the name of the domain found, the description, the p-value and the pFam score for the identified domain within the sequence.

The nucleotide sequence within the sequences that codes for signal peptide sequences and their cleavage sites can be determine from using Neural Network SignalP V1.1 program (from Center for Biological Sequence Analysis, The Technical University of Denmark). The process for identifying prokaryotic and eukaryotic signal peptides and their cleavage sites are also disclosed by Henrik Nielson, Jacob Engelbrecht, Soren Brunak, and Gunnar von Heijne in the publication "Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites" Protein Engineering, Vol. 10, no. 1, pp. 1-6 (1997), incorporated herein by reference. A maximum S score and a mean S score, as described in the Nielson et as reference, was obtained for the polypeptide sequences. Table 5 shows the position of the signal peptide in each of the polypeptides and the maximum score and mean score associated with that signal peptide.

Table 6 is a correlation table of all of the sequences and the SEQ ID NOS.

### TABLE 1

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:
adult brain	<u> </u>		3 15 19 74 88 174
			212-213 229
adult brain	GIBCO	ABD003	1-4 14 33 44 57 73-74
			78 88 108 145 148
			174 196 209-213 215
			218 235
adult brain	Clontech	ABR001	8 118 145 155 174
			192 208
adult brain	Clontech	ABR006	2 25 35-36 214 220
adult brain	Clontech	ABR008	1 4 13-14 16 25 33
			35-36 41-43 45 50 56
			65 80 86 88 95 108
			110-112 118 129 141
			145 158-159 162 164
			169-171 173-174 189
			196 208-211 215 218-
			220 222-223 228
adult brain	Clontech	ABR011	211
adult brain	Invitrogen	ABR013	48 109 121 158-159
			199
adult brain	Invitrogen	ABT004	3-4 14 35-36 88 145
			174 196 210-211 222
			224 228
cultured preadipocytes	Strategene	ADP001	2 6-8 13 69 73 193
			210 212-213 225 229
adrenal gland	Clontech	ADR002	3-4 7-8 12-14 21 33
			38 48 54 74 81 86-87
,			145 158-159 163 208 211-213 221 229 235
adult heart	GIBCO	AHR001	1-2 9 11 14-15 33 37
adult ficalt	GIBCO	Ankovi	39-41 61-62 73-75
			102 145-146 148 187
			196 210-213 218 222
			224-225 235
adult kidney	GIBCO	AKD001	1-4 8 10 12 14-15 33-
			34 37 39-40 43-48 54
			59 73-74 79-80 88
			107-108 118 121 138
			145 159 163 169-171
			173-174 186 196 209-
			215 224 229 235
adult kidney	Invitrogen	AKT002	1 8 12 14 35-36 47-48
			86 118 130 148 158-
			159 196 210 222-223
			225 235
adult lung	GIBCO	ALG001	12 16 37 56 73 88 96-
			99 106 114 145 148
			155 164 216-217 228-
	<u> </u>		229

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:
lymph node	Clontech	ALN001	12 41 47-48 94 96-99
•			107-109 121 145 158-
			159 172 191
young liver	GIBCO	ALV001	3 8 14 39-40 48 58 64
•			66 86 104 108 140
			145 158-160 169-171
			174 189 211-214 216-
	į	_	217 229 235
adult liver	Invitrogen	ALV002	4 16 37 39-40 66 73
			86 105 145 169-171
			173 189 192 194-196
			209 211 214 222 224
			228
adult liver	Clontech	ALV003	214
adult ovary	Invitrogen	AOV001	1 3-4 7 11-16 18 20
•			34-37 39-40 42-45 48
		1	57-59 70-74 76 78 80
		}	88 96-99 102 108 118
		į	140-141 145-148 155
			157-160 162-164
			172-175 182 187 196
		Į.	209-213 220-222 225
			228-229 235
adult placenta	Invitrogen	APL001	14 45 222
placenta	Invitrogen	APL002	55 138
adult spleen	GIBCO	ASP001	2-4 8 11-12 33 39-40
•			44 47-48 74 80 96-99
		<b>,</b>	107-110 121 145 155
•			158-159 164 172 174
			191 211-213 216-217
	·		222 229 235
testis	GIBCO	ATS001	2 35-37 39-40 175
			196 212-213 235
adult bladder	Invitrogen	BLD001	5 7-8 14 73 138 141
			159 196 235
bone marrow	Clontech	BMD001	2 4 7 12 19 39-40 47-
			48 57 63 74 80 94 96-
i			99 103 107-108 118
			121 140 145 149 156
			158-160 169-172 186
			191 210 212-213 215
			229
bone marrow	Clontech	BMD002	1 4 12 14 33 35-36 41
			44-45 47-48 74 88
			96-99 107-108 110
			118 158-160 173 190-
			191 209 212-213 223
bone marrow	Clontech	BMD004	7 48 96-99 158-159
			212-213
adult colon	Invitrogen	CLN001	2 11-12 80 96-99 140
•			191

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:	
adult cervix	BioChain	CVX001	1-2 12 14-15 26 33	
			35-36 39 42-43 47 54	
			73 80 88 95 107 129-	
	,		137 150 196 212-213	
	·		220-221 224 227-229	
			235	
endothelial cells	Strategene	EDT001	2 4 8 14 33-36 39-40	
			42-43 56 67-69 73-74	
			80 88 95 108-109 116	
			121 132 140 145 163	
			173 209 211-213 223	
			225 228-229	
Genomic clones from	Genomic DNA from	EPM001	206-207	
the short arm of	Genetic Research			
chromosome 8				
Genomic clones from	Genomic DNA from	EPM003	207	
the short arm of	Genetic Research			
chromosome 8	Conous resources			
Genomic clones from	Genomic DNA from	EPM004	207	
the short arm of	Genetic Research			
chromosome 8	Genetic recount.			
fetal brain	Clontech	FBR006	2 4 8 25 41 74 111-	
Total Oralli	Cionton		112 141 143 162 187	
			196 210-213 215-217	
			219-220 222-223 228	
fetal brain	Invitrogen	FBT002	4 14 16 18 35-36 65	
Total orani	in the Bon		74 78 80 111-112 139	
			157 173-174 196 209-	
			211 220-221	
fetal kidney	Clontech	FKD001	7 33 46 65 108 211-	
Total Interior			213	
fetal kidney	Clontech	FKD002	80 212-213	
fetal lung	Clontech	FLG001	108 118 155	
fetal lung	Invitrogen	FLG003	3 39-40 145 211 222	
fetal liver-spleen	Columbia University	FLS001	1-4 7-8 10 14-17 22	
Total II voi opioon			28 33-40 42-44 48	
			52-53 60 66 68 74 88	
			96-99 102 108 110-	
			112 117 136 138 140	
			143 145 148 154 158-	
· ·			159 163 169-172 174	
			181 191 196 201 209-	
			217 220 222-224 228-	
			229 231 235	
fetal liver-spleen	Columbia University	FLS002	1-2 7-8 11 14-15 27-	
l service opinion			28 33-37 39-40 44 53	
			60 68 73-75 80 86 91	
			95 108 110 115 122-	
	•		128 138 140 143 145	
<b>‡</b>	1	Į.	154-155 164 169-172	
			134-133 104 107-172	

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:	
113340 0118		<del>                                     </del>	200-205 209 212-214	
			216-217 220 222-225	
			230-231 235	
fetal liver-spleen	Columbia University	FLS003	214 223-224	
fetal liver	1		3 8 41 66 73-74 80 88	
1011111101			95 108 110 145 148	
			154 169-171 173 196	
			211 214	
fetal liver	Clontech	FLV004	7	
fetal muscle	Invitrogen	FMS001	7 11 14 37 43 79 139	
2000.			196 211 224-225 228	
fetal muscle	Invitrogen	FMS002	7	
fetal skin	Invitrogen	FSK001	7-8 14 33 35-37 39 74	
1000.	3		88 108 142 162 172-	
			175 196 210-213 215	
			220 222	
fetal skin	Invitrogen	FSK002	7 196 235	
fetal spleen	BioChain	FSP001	8 96-99	
umbilical cord	BioChain	FUC001	7 13-14 20 37 56 102	
			108 113 145 148 160	
	1		176-180 199 209 212-	
			213 222	
fetal brain	GIBCO	HFB001	2 13-15 37 42-43 57	
			73 88 108 111-112	
			118 129 163 174 192	
			196 199 208-213 215	
			224-225 229 235	
macrophage	Invitrogen	HMP001	44	
infant brain	Columbia University	IB2002	1 8 14 16 31 37 57 64	
			77 80 88 108 111-112	
			151 162 174 192 196	
			210-213 215 223 225	
			229	
infant brain	Columbia University	IB2003	7 31 57 88 94 148	
			162 174 196-198 210-	
	į	IBM002	213 215 224-225	
infant brain	brain Columbia University		8	
infant brain	Columbia University	IBS001	31 42-43 111-112 196	
			211	
Lung, fibroblast	Strategene	LFB001	4 73 174 196 199 222	
lung tumor	Invitrogen	LGT002	2-3 5 7-9 11-12 14 22	
	ļ		24 37 39-40 42-44	
			47-48 57 73 86 102	
			106 109-110 121 140	
			145 148 155 158-160	
			162 164-166 169-171	
			186 196 209-213 216-	
			218 220 222-223 228	
lymphocytes	ATCC	LPC001	13 30 39-40 42-44	
			119 153 158-159 186-	
			188 209 211 222 226	

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:
	-		232-234 236
leukocyte	GIBCO	LUC001	4-5 11 13 16 29-30 32
•			34 39-41 44 47-51 57
			74 80 88 96-99 107-
			110 116 121 129 145
			148 152-155 158-160
			163-164 172 186 190-
			191 196 210-213 216-
			217 219 229 235
leukocyte	Clontech	LUC003	109 121 145 155 160
			212-213 235
melanoma from cell line ATCC #CRL 1424	Clontech	MEL004	2 4 22 33 140 192 199 211-213 222 228
mammary gland	Invitrogen	MMG001	1-2 4 7-8 12 14 22
, 0			35-37 39-40 42-44
			47-48 51 59 73-74 80
			88 96-99 107 109 116
•			121 138 145 148 162
			167-174 191-192 196
			209-213 215 218 221-
			222 224-225 228
induced neuron cells	Strategene	NTD001	163 192 209 224
retinoid acid induced neuronal cells	Strategene	NTR001	211-213 223
neuronal cells	Strategene	NTU001	2 8 14 39-40 209 211
			215 224
placenta	Clontech	PLA003	145
prostate	Clontech	PRT001	4 8 14 211 218 229 235
rectum	Invitrogen	REC001	12 14 48 73 96-99
			143 158-159 169-171
			174 196 211 224-225
salivary gland	Clontech	SAL001	4 12 37 47-48 70 74
			107 109 114 121 144
			158-159 174 196 212-
		GDIOOI	213 220
small intestine	Clontech	SIN001	12 39-40 47 74 82-83 89-90 96-99 107 117-
			118 173 191 222 224
			229 235
skeletal muscle	Clontech	SKMs04	88
spinal cord	Clontech	SPC001	1 4 14 27 88 91-92
spinai colu	Cioniccii	SECOUL	108 119-120 145 174
			212-213 220 235
adult spleen	Clontech	SPLc01	158-159 219 229 235
stomach	Clontech	STO001	4 37 48 93-95 115
			138 159 216-217
thalamus	Clontech	THA002	37 94 125 139 174
thymus	Clontech	THM001	8 12 22 25 39-40 84
			118 149 160 172 174

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:	
			191 212-213 222	
thymus	Clontech	THMc02	4-5 14 33 42-44 48 50	
			57 59 73-74 78 96-99	
			109 121 141 145 148	
			155-162 172 187 191	
			210 212-213 219 223	
			228	
thyroid gland	Clontech	THR001	4 8-9 14 23 37 39-40	
,			48 54 57 74 86 100-	
		•	101 107 118 140 159	
			169-171 196 209-211	
			225 229 235	
trachea	Clontech	TRC001	11 37 48 85 95-99	
			114 118 159 172 191	
			212-213	
uterus	Clontech	UTR001	8 102-103 227 235	

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TABLE 2

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID NO:	NUMBER			WATERMAN SCORE	IDENTITY
1	AJ222644	Arabidopsis thaliana	asparaginyl-tRNA synthetase	659	50
2	Y57899	Homo sapiens	Human transmembrane protein HTMPN-23.	2044	99
3	Y20291	Homo sapiens	Human apolipoprotein E wild type protein fragment 1.	1080	91
4	D42138	Homo sapiens	PIG-B	3001	100
5	AF148145	Mus musculus	putative thymic stromal co-transporter TSCOT	1459	78
6	X68657	Rattus norvegicus	granzyme-like protein II	1138	89
7	Z74615	Homo sapiens	prepro-alpha1(I) collagen	8216	99
8	D13623	Rattus sp.	p34 protein	1482	94
9	Y94263	Homo sapiens	Human phospholipid binding protein 2, PLBP2.	1185	99
11	Y29939	Homo sapiens	Human retinol dehydrogenase type II homologue.	1663	100
12	Y14738	Homo sapiens	immunoglobulin lambda light chain	1144	91
13	AF156549	Mus musculus	putative E1-E2 ATPase	4825	79
14	Y00815	Homo sapiens	put. LAR preprotein (AA -16 to 1881)	9947	99
19	Y11584	Homo sapiens	Human 5' EST secreted protein SEQ ID NO:236.	192	100
25	Y70210	Homo sapiens	Human TANGO 130 protein.	991	95
31	D26093	Gallus gallus	VMO-I	463	52
32	AE000658	Homo sapiens	TCRAV4S1	558	100
33	W64542	Homo sapiens	Human stomach cancer cell clone HP10071 protein.	483	100
34	Y87342	Homo sapiens	Human signal peptide containing protein HSPP- 119 SEQ ID NO:119.	690	100
35	AL049795	Homo sapiens	dJ622L5.8.1 (novel protein (isoform 1))	399	96
36	AL049795	Homo sapiens	dJ622L5.8.1 (novel protein (isoform 1))	458	100

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SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID NO:	NUMBER			WATERMAN SCORE	IDENTITY
37	Y44273	Homo	Human Metabotropic	2458	99
		sapiens	Glutamate Receptor-like		
			protein, MGRcm.		
39	AF111713	Homo	junctional adhesion	1544	100
		sapiens	molecule		
40	AF154005	Homo	junction adhesion	1333	100
		sapiens	molecule		
41	Y35960	Homo	Extended human secreted	500	98
		sapiens	protein sequence, SEQ ID NO. 209.		
42	AF247174	synthetic	RP6-alkaline	140	36
		construct	phosphatase hybrid		
			protein		
43	AF179415	Dendroides canadensis	antifreeze protein 11	132	30
44	W01049	Homo	Product of 200 gene	1580	99
		sapiens	differentially expressed		
		1	in T helper cells.		
45	AL121929	Homo	bA416N2.2 (similar to	5039	100
		sapiens	murine FISH (an SH3		1
		_	and PX domain-		
	}		containing protein, and		
			Src substrate))		<u> </u>
47	X57816	Homo	immunoglobulin lambda	1212	100
		sapiens	light chain	21.62	06
48	W88464	Homo	Monoclonal antibody	2162	86
		sapiens	4B5 heavy chain variable		
50	17000500	<u> </u>	region.	280	54
50	AE003523	Drosophila	CG7510 gene product	280	34
		melanogaste			
54	AF231128	Danio rerio	Donth	165	42
55	AB047612	Macaca	Dap1b hypothetical protein	330	98
33	AB047012	fascicularis	hypothetical protein	330	
56	Y41701	Homo	Human PRO708 protein	1070	99
		sapiens	sequence.		
65	Y73351	Homo	HTRM clone 1484257	104	39
	1,000	sapiens	protein sequence.		
66	AF188285	Homo	bone morphogenetic	2266	100
		sapiens	protein 9		
73	AE002038	Deinococcu	ribosomal protein L20	202	41
		s	1	}	
		radiodurans			
74	AF157321	Homo	30 kDa protein	1252	99
		sapiens	_		
79	AC004522	Homo	gap junction protein;	482	93
		sapiens	similar to P36383		
			(PID:g544117)		

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID NO:	NUMBER	·		WATERMAN SCORE	IDENTITY
80	AL355715	Homo sapiens	PCD9	2075	100
86	Y76140	Homo sapiens	Human secreted protein encoded by gene 17.	692	97
88	AL020993	Homo sapiens	dJ5O6.2 (novel protein similar to C. elegans F40E10.6 (isoform 1))	1545	100
91	AC004896	Homo sapiens	similar to contactin associated protein; similar to U87223 (PID:g1857708)	157	58
92	G00517	Homo sapiens	Human secreted protein, SEQ ID NO: 4598.	124	54
94	Y27593	Homo sapiens	Human secreted protein encoded by gene No. 27.	248	58
95	Y92507	Homo sapiens	Human OXRE-4 with identity to 3-oxo-5-alphasteroid dehydrogenase.	1715	100
96	AJ006112	Homo sapiens	anti-(ED-B) scFV	1238	100
97	AF174012	Homo sapiens	immunoglobulin heavy chain variable region precursor	692	91
98	AJ006111	Homo sapiens	anti-(ED-B) scFV	1166	93
99	AJ006112	Homo sapiens	anti-(ED-B) scFV	1046	84
102	AF137378	Homo sapiens	integrin alpha 11 subunit precursor	6224	99
106	W62068	Homo sapiens	Human lung tissue gene LU103 protein.	333	97
107	X57802	Homo sapiens	immunoglobulin lambda light chain	1160	95
108	Y41697	Homo sapiens	Human PRO700 protein sequence.	1441	100
109	M12886	Homo sapiens	T-cell receptor beta chain	1590	98
110	U71383	Homo sapiens	OB binding protein-2	2913	99
111	AB035356	Homo sapiens	neurexin I-alpha protein	4390	76
112	L14851	Rattus norvegicus	neurexin III-alpha	5614	97
114	X60660	Rattus rattus	potential ligand-binding protein	382	27
116	L03785	Homo sapiens	myosin regulatory light chain	873	100
118	Y58637	Homo	Protein regulating gene	246	30

SEQ ID NO:	ACCESSION NUMBER	SPECIES	DESCRIPTION	SMITH- WATERMAN SCORE	% IDENTITY
		sapiens	expression PRGE-30.		
121	M12886	Homo sapiens	T-cell receptor beta chain	1536	96
129	AL031985	Homo sapiens	dJ228H13.3 (zinc finger protein)	2364	100
138	Y59664	Homo sapiens	Secreted protein 108- 004-5-0-E8-FL.	973	98
139	AF139980	Homo sapiens	LW-I	2275	100
140	Y28279	Homo sapiens	Human G-protein coupled receptor GRIR-1.	742	100
141	AF287892	Homo sapiens	sialic acid binding immunoglobulin-like lectin 8 long splice variant	1320	96
145	X00699	Homo sapiens	precursor	1400	98
146	AB036849	Ciona intestinalis	fibrinogen-like protein	184	40
148	W78169	Homo sapiens	Human secreted protein encoded by gene 44 clone HETFJ05.	2114	98
154	AF109683	Homo sapiens	leukocyte-associated Ig- like receptor 1b	174	25
155	W99070	Homo sapiens	Human PIGR-1.	434	53
158	AF184764	Homo sapiens	IgG1 heavy chain	939	79
159	Y14737	Homo sapiens	immunoglobulin lambda heavy chain	2559	100
160	AF043171	Homo sapiens	T cell receptor alpha chain	1479	100
162	AB000199	Rattus norvegicus	CCA2 protein	822	87
163	AF186273	Homo sapiens	leucine-rich repeats containing F-box protein FBL3	251	32
164	AF227924	Homo sapiens	sialic acid-binding lectin Siglec-9	2459	99
167	AF098807	Homo sapiens	lipoma HMGIC fusion partner	713	63
168	AF098807	Homo sapiens	lipoma HMGIC fusion partner	443	57
169	Y66706	Homo sapiens	Membrane-bound protein PRO1129.	2786	99
170	Y66706	Homo sapiens	Membrane-bound protein PRO1129.	1733	98

SEQ ID	ACCESSION NUMBER	SPECIES	DESCRIPTION	SMITH- WATERMAN	% IDENTITY
NO:				SCORE	
171	Y66706	Homo sapiens	Membrane-bound protein PRO1129.	1058	93
173	W67898	Homo sapiens	Human secreted protein encoded by gene 16 clone HE9DG49.	838	95
174	Y06115	Homo sapiens	Human organic cation transporter OCT-3.	1876	100
182	G02872	Homo sapiens	Human secreted protein, SEQ ID NO: 6953.	262	59
186	AE003652	Drosophila melanogaste r	CG17996 gene product	115	66
187	AF166350	Homo sapiens	ST7 protein	4716	100
189	AF202889	Homo sapiens	regeneration associated protein 3	1864	100
191	AF090418	Homo sapiens	scFV anitbody V-region	1010	85
192	AJ010231	Homo sapiens	RET finger protein-like 2	1522	100
193	U65579	Homo sapiens	mitochondrial NADH dehydrogenase- ubiquinone Fe-S protein 8, 23 kDa subunit precursor	981	89
196	AF161444	Homo sapiens	HSPC326	1467	96
199	D26179	Rattus norvegicus	V-1 protein	479	100
208	L22031	Glycine max	hydroxyproline-rich glycoprotein	99	34
209	AF201931	Homo sapiens	DC1	1662	99
210	W74882	Homo sapiens	Human secreted protein encoded by gene 154 clone HE6FL83.	480	100
211	U53925	Mus musculus	transcription factor C1 (HCF)	297	31
212	AJ251914	Sus scrofa	putative RNA helicase	2199	100
213	AJ251914	Sus scrofa	putative RNA helicase	1571	100
214	X04494	Homo sapiens	precursor polypeptide	1903	100
215	Y66699	Homo sapiens	Membrane-bound protein PRO1108.		100
216	AJ130710	Homo sapiens	QA79 membrane protein, allelic variant airm-1b	2473	100
217	AJ130711	Homo sapiens	QA79 membrane protein, splice product airm-2	1969	100

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID	NUMBER			WATERMAN	IDENTITY
NO:				SCORE	1.00
218	AF233523	Homo	beta V spectrin	18612	99
		sapiens			126
219	AF127481	Homo	non-ocogenic Rho	743	36
		sapiens	GTPase-specific GTP exchange factor		
220	Y71066	Homo	Human membrane	2378	99
		sapiens	transport protein, MTRP-		
			11.		
221	AF132730	Homo	unknown	1899	100
		sapiens		1004	100
223	W54097	Homo	Homo sapiens B223	1834	99
		sapiens	sequence.	1017	100
224	Y99449	Homo	Human PRO1760	1017	100
	1	sapiens	(UNQ833) amino acid sequence SEQ ID		
			NO:376.		
225	Y92368	Homo	G protein-coupled	2293	100
223	1 92300	sapiens	receptor protein 8.		
227	Y99436	Homo	Human PRO1474	464	100
		sapiens	(UNQ745) amino acid		
		1	sequence SEQ ID		}
			NO:334.		
228	AK024825	Homo	unnamed protein product	1375	99
		sapiens			
229	G03186	Homo	Human secreted protein,	307	96
		sapiens	SEQ ID NO: 7267.		1
235	AB025606	Arabidopsis	contains similarity to	753	46
		thaliana	GTPase activating		
	<u> </u>	<u> </u>	protein~gene_id:F6N7.7		]

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## TABLE 3

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
1	PF00152	tRNA synthetases class II.	PF00152D 21.30 8.364e-28 422-461 PF00152C 28.03 9.250e-21 220-257 PF00152B 15.67 2.658e-13 159-184 PF00152A 19.68 5.714e-11 44-67
2	PR00237	RHODOPSIN-LIKE GPCR SUPERFAMILY SIGNATURE	PR00237F 13.57 5.263e-09 158-183
3	PD02807	APOLIPOPROTEIN E PRECURSOR APO-E GLYCOPROTEIN PLAS.	PD02807B 8.27 1.000e-40 64-103 PD02807C 8.91 1.000e-40 139-188 PD02807D 7.99 1.000e-40 188-238 PD02807A 12.43 6.143e-25 27-48 PD02807C 8.91 5.645e-09 95-144
5	PD01572	PHOTOSYSTEM II REACTION CENTRE T PROTEIN PHOTOS.	PD01572 8.77 6.917e-09 213-243
6	BL00134	Serine proteases, trypsin family, histidine proteins.	BL00134A 11.96 2.125e-15 50-67 BL00134B 15.99 7.618e-13 195-219
7	DM01418	352 FIBRILLAR COLLAGEN CARBOXYL- TERMINAL.	DM01418A 20.83 1.000e-40 1252-1300 DM01418B 22.51 1.000e-40 1351-1393 DM01418C 20.48 5.500e-40 1422-1464
8	BL00224	Clathrin light chain proteins.	BL00224B 16.94 1.082e-09 166-219
9	BL01220	Phosphatidylethanolamine- binding protein family proteins.	BL01220B 16.65 6.774e-23 85-126 BL01220C 14.75 5.857e-17 130-158
11	PR00081	GLUCOSE/RIBITOL DEHYDROGENASE FAMILY SIGNATURE	PR00081C 15.13 5.846e-11 151-168
12	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 1.529e-14 159-182 BL00290B 13.17 9.000e-12 219-237
13	PR00121	SODIUM/POTASSIUM- TRANSPORTING ATPASE SIGNATURE	PR00121D 16.72 2.694e-12 113-135
14	PR00700	PROTEIN TYROSINE PHOSPHATASE SIGNATURE	PR00700B 16.80 1.500e-24 1420-1441 PR00700D 12.47 4.214e-22 1543-1562 PR00700B 16.80 4.240e-21 1709-1730 PR00700D 12.47 7.158e-20 1834-1853 PR00700C 13.17 5.800e-18 1504-1522 PR00700C 13.17 7.353e-17 1793-1811 PR00700E 17.57 4.000e-14 1865-1881 PR00700F 11.18 7.353e-13 1590-1601 PR00700F 11.18 1.429e-12 1881-1892 PR00700E 17.57 5.304e-12 1574-1590 PR00700A 6.96 8.714e-11 1404-1412
31	PD02382	RECEPTOR CHAIN PRECURSOR	PD02382B 4.60 7.000e-09 105-112

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
		TRANSME.	
37	BL00979	G-protein coupled receptors family 3 proteins.	BL00979L 20.63 2.485e-09 150-191
39	DM00179	w KINASE ALPHA ADHESION T-CELL.	DM00179 13.97 1.000e-11 102-112
40	DM00179	w KINASE ALPHA ADHESION T-CELL.	DM00179 13.97 1.000e-11 62-72
45	BL50002	Src homology 3 (SH3) domain proteins profile.	BL50002B 15.18 3.000e-09 953-967
47	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 1.529e-14 150-173 BL00290B 13.17 9.000e-12 210-228
48	DM00031	IMMUNOGLOBULIN V REGION.	DM00031A 16.80 9.775e-36 20-68 DM00031B 15.41 7.600e-21 84-118 DM00031C 12.79 8.929e-10 131-142
56	BL00523	Sulfatases proteins.	BL00523C 12.64 4.000e-13 314-325 BL00523A 13.36 7.300e-13 222-239 BL00523B 8.64 6.114e-11 268-280
65	BL00028	Zinc finger, C2H2 type, domain proteins.	BL00028 16.07 4.115e-11 204-221
66	BL00250	TGF-beta family proteins.	BL00250A 21.24 3.000e-24 327-363 BL00250B 27.37 1.000e-15 393-429
73	PR00062	RIBOSOMAL PROTEIN L20 SIGNATURE	PR00062C 16.68 7.245e-15 82-109 PR00062B 16.66 2.658e-11 49-79
79	BL00407	Connexins proteins.	BL00407E 22.17 8.820e-23 169-214 BL00407B 14.23 6.311e-20 39-70 BL00407C 14.61 1.164e-18 70-98 BL00407A 18.57 6.250e-13 2-39 BL00407D 17.61 5.790e-12 131-161
96	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 3.520e-10 281-304
97	DM00031	IMMUNÔGLOBULIN V REGION.	DM00031A 16.80 1.000e-40 20-68 DM00031B 15.41 1.000e-36 84-118 DM00031C 12.79 1.600e-15 127-138
98	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 3.520e-10 286-309
99	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290B 13.17 4.000e-12 341-359 BL00290A 20.89 3.520e-10 280-303
102	PR00453	VON WILLEBRAND FACTOR TYPE A DOMAIN SIGNATURE	PR00453A 12.79 9.719e-13 163-181 PR00453B 14.65 1.818e-12 200-215 PR00453C 12.26 3.769e-10 265-274
107	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 1.563e-15 151-174 BL00290B 13.17 9.000e-12 211-229
108	BL00194	Thioredoxin family proteins.	BL00194 12.16 2.565e-13 46-59 BL00194 12.16 3.348e-13 179-192

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
109	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 8.200e-12 160-183
111	DI 00064	Syndecans proteins.	BL00964B 12.05 2.604e-10 981-1024
111	BL00964	Syndecans proteins.  Syndecans proteins.	BL00964B 12.05 2.604e-10 1011-1054
112	BL00964	LBP / BPI / CETP family	BL00400D 23.26 7.222e-12 251-288
114	BL00400	proteins.	
116	BL00018	EF-hand calcium-binding	BL00018 7.41 1.391e-09 43-56
116	BLOODIS	domain proteins.	BE00010 7.41 1.5710.07 43 30
121	BL00290	Immunoglobulins and	BL00290A 20.89 8.200e-12 159-182
121	BE00290	major histocompatibility complex proteins.	BE002901120.09 0.2000 12 109 102
129	BL00028	Zinc finger, C2H2 type,	BL00028 16.07 8.875e-15 347-364
		domain proteins.	BL00028 16.07 6.824e-14 207-224
			BL00028 16.07 7.353e-14 403-420
			BL00028 16.07 8.650e-13 235-252
	1		BL00028 16.07 8.435e-12 319-336
			BL00028 16.07 3.077e-11 291-308 :
			BL00028 16.07 3.769e-11 263-280
		1	BL00028 16.07 5.154e-11 179-196
	1		BL00028 16.07 4.000e-10 375-392
132	PR00836	SOMATOTROPIN	PR00836B 16.59 8.347e-09 3-22
		HORMONE FAMILY	
		SIGNATURE	
139	PR00056	HEAT SHOCK FACTOR (HSF) DOMAIN SIGNATURE	PR00056C 14.47 7.823e-12 153-166
140	PR00245	OLFACTORY	PR00245A 18.03 7.300e-19 82-104
140	1 K00243	RECEPTOR SIGNATURE	
145	PF00969	Class II histocompatibility	PF00969B 9.97 1.000e-40 58-94
		antigen, beta domain	PF00969C 27.72 1.000e-40 97-147
		proteins.	PF00969E 11.49 1.000e-39 212-247
	1		PF00969A 22.07 3.520e-38 12-55
			PF00969D 14.02 4.789e-36 154-184
146	BL00514	Fibrinogen beta and	BL00514C 17.41 2.579e-24 181-218
		gamma chains C-terminal	BL00514G 15.98 9.111e-12 262-292
1.55	D) (01 (00	domain proteins.	DM01688B 15.06 3.628e-09 82-130
155	DM01688	2 POLY-IG RECEPTOR.	DM01688B 15.06 3.628e-09 82-130 DM00031A 16.80 1.000e-40 20-68
158	DM00031	IMMUNOGLOBULIN V	DM00031A 16.80 1.000e-40 20-68 DM00031B 15.41 5.865e-25 86-120
		REGION.	DM00031B 13.41 3.8636-23 86-120 DM00031C 12.79 4.429e-10 129-140
150	D) (00001	IMMUNOGLOBULIN V	DM00031C 12.79 4.4296-10 129-140  DM00031A 16.80 1.000e-40 20-68
159	DM00031	REGION.	DM00031A 16.80 1.000e-40 20-68 DM00031B 15.41 1.000e-40 84-118
		REGION.	DM00031B 13.41 1.000e-40 84-118 DM00031C 12.79 1.600e-15 134-145
160	DM00031	IMMUNOGLOBULIN V	DM00031B 15.41 6.294e-12 85-119
		REGION.	
162	PF01073	3-beta hydroxysteriod	PF01073A 18.01 9.206e-22 140-193
		dehydrogenase/isomerase	PF01073B 12.26 6.831e-19 222-267
160	DIOCOCC	family.	PF01073C 10.62 2.645e-17 322-370
169	BL00086	Cytochrome P450 cysteine	BL00086 20.87 3.813e-24 480-512

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
		heme-iron ligand proteins.	
170	BL00086	Cytochrome P450 cysteine	BL00086 20.87 3.813e-24 502-534
.,,		heme-iron ligand proteins.	
171	BL00086	Cytochrome P450 cysteine	BL00086 20.87 3.813e-24 363-395
171	BECOOL	heme-iron ligand proteins.	
173	BL00453	FKBP-type peptidyl-prolyl	BL00453B 23.86 3.000e-20 87-121
173	DE00433	cis-trans isomerase	BL00453A 15.57 9.379e-10 63-78
		proteins.	
174	BL00216	Sugar transport proteins.	BL00216B 27.64 4.900e-10 240-290
187	BL01209	LDL-receptor class A	BL01209 9.31 5.500e-11 470-483
10/	BLU1209	(LDLRA) domain proteins.	BL01209 9.31 2.212e-10 395-408
		(LDLKA) domain proteins.	BL01209 9.31 6.365e-10 433-446
			BL01209 9.31 8.962e-10 239-252
	DD01733	APOLIPOPROTEIN	PD01733B 20.44 6.600e-14 109-164
189	PD01733		PD01753B 20.44 0.000C-14 107-104
		PLASMA LIPID	
		TRANSPORT H.	PR00237E 13.03 8.412e-09 15-39
190	PR00237	RHODOPSIN-LIKE	PR0023/E 13.03 8.412e-09 13-39
		GPCR SUPERFAMILY	
		SIGNATURE	D) (00001 + 1 ( 00 1 000 + 40 (1 100
191	DM00031	IMMUNOGLOBULIN V	DM00031A 16.80 1.000e-40 61-109
		REGION.	DM00031B 15.41 1.000e-40 125-159
			DM00031C 12.79 1.600e-15 174-185
			DM00031B 15.41 9.544e-09 245-279
192	PF00622	Domain in SPla and the	PF00622B 21.00 8.250e-11 161-183
		RYanodine Receptor.	
193	BL00198	4Fe-4S ferredoxins, iron-	BL00198 10.43 5.263e-12 152-164
		sulfur binding region	BL00198 10.43 1.346e-10 113-125
		proteins.	
199	PF00023	Ank repeat proteins.	PF00023A 16.03 8.000e-12 90-106
208	BL00127	Pancreatic ribonuclease	BL00127C 31.49 7.288e-09 33-77
		family proteins.	
210	BL01310	ATP1G1/PLM/MAT8	BL01310 14.74 2.432e-29 71-107
İ		family proteins.	
212	BL00039	DEAD-box subfamily	BL00039D 21.67 5.000e-26 340-386
		ATP-dependent helicases	BL00039A 18.44 6.114e-17 64-103
1		proteins.	BL00039B 19.19 3.681e-11 104-130
213	BL00039	DEAD-box subfamily	BL00039D 21.67 5.000e-26 314-360
		ATP-dependent helicases	BL00039A 18.44 6.114e-17 64-103
		proteins.	BL00039B 19.19 3.681e-11 104-130
214	BL00280	Pancreatic trypsin inhibitor	BL00280 24.61 6.727e-38 238-282
'	1	(Kunitz) family proteins.	BL00280 24.61 1.514e-30 294-338
216	PF00064	Neuraminidases.	PF00064D 17.65 8.830e-09 11-50
217	PF00064	Neuraminidases.	PF00064D 17.65 8.830e-09 11-50
218	BL00019	Actinin-type actin-binding	BL00019D 15.33 7.585e-21 196-226
210	DEVIVITY	domain proteins.	BL00019D 13:35 7:3636-21 136 226 BL00019C 14.66 9.143e-20 128-164
		domain proteins.	BL00019A 12.56 5.408e-12 56-67
	1		BL00019A 12.30 3.408c-12 30-07 BL00019B 13.34 9.795e-12 83-106
210	DD00104	TROPOMYOCRI	PR00194D 9.57 1.240e-10 391-415
219	PR00194	TROPOMYOSIN SIGNATURE	TRUUT74D 7.37 1.2406-10 371-413
<u></u>		SIGNATURE	

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
220	BL00594	Aromatic amino acids permeases proteins.	BL00594A 16.75 4.743e-09 56-100
222	BL00415	Synapsins proteins.	BL00415N 4.29 8.695e-10 335-379
223	PR00217	43 KD POSTSYNAPTIC PROTEIN SIGNATURE	PR00217C 10.91 7.725e-09 302-318
225	PD02918	AMINOGLYCOSIDE N3'- ACETYLTRANSFERASE III.	PD02918A 18.79 3.621e-09 345-385
227	BL00282	Kazal serine protease inhibitors family proteins.	BL00282 16.88 4.717e-18 45-68
235	PR00356	TYPE II ANTIFREEZE PROTEIN SIGNATURE	PR00356G 10.80 8.644e-09 536-550

<sup>\*</sup> results include in order: accession number subtype, raw score; p-value; position of signature in amino acid sequence.

TABLE 4

SEQ	PFAM NAME	DESCRIPTION	p-value	PFAM
D D	A A A AATA A 14 AATAAA			SCORE
10:				
10.	tRNA-synt_2	tRNA synthetases class II (D, K and	1.1e-84	294.8
		N)		
3	Apolipoprotein	Apolipoprotein A1/A4/E family	7.3e-91	315.3
5	trypsin	Trypsin	2.9e-59	189.2
<del>,</del> 7	Collagen	Collagen triple helix repeat (20	4.1e-290	977.2
,	Collagell	copies)		
8	LRR	Leucine Rich Repeat	2.9e-13	57.5
9	PBP	Phosphatidylethanolamine-binding	1.4e-17	71.9
,	1.51	protein		
11	adh_short	short chain dehydrogenase	7e-43	155.9
12		Immunoglobulin domain	2.1e-14	51.4
14	ig Y_phosphatase	Protein-tyrosine phosphatase	4.8e-299	1006.8
25	SH3	SH3 domain	0.026	5.2
23 32		Immunoglobulin domain	1.8e-09	35.6
32 37	ig 7tm 3	7 transmembrane receptor	7.2e-09	29.0
37 39		Immunoglobulin domain	1.4e-20	71.3
<del>39</del> 40	ig	Immunoglobulin domain	2.6e-15	54.4
<del>40</del> 45	ig SH3	SH3 domain	1.4e-42	154.9
<del>45</del> 47		Immunoglobulin domain	2.5e-16	57.7
	ig	Immunoglobulin domain	1.6e-24	84.1
48 65	ig zf-C2H2	Zinc finger, C2H2 type	2.7e-06	34.3
66 66	TGF-beta	Transforming growth factor beta like	6.9e-64	197.9
		Ribosomal protein L20	2e-22	74.0
73	Ribosomal_L20 connexin	Connexin	1.6e-50	181.3
79		Immunoglobulin domain	2.5e-26	89.9
96	ig	Immunoglobulin domain	1.5e-08	32.6
97	ig	Immunoglobulin domain	3.6e-25	86.1
98	ig	Immunoglobulin domain	7.6e-33	110.9
99	ig	FG-GAP repeat	6.9e-66	232.3
102	FG-GAP	Immunoglobulin domain	1.3e-16	58.6
107	ig	Thioredoxin	2.8e-79	267.1
108	thiored	Immunoglobulin domain	2.9e-16	57.5
109	ig		4.6e-13	47.1
110	ig	Immunoglobulin domain Laminin G domain	2.4e-63	223.9
111	laminin_G		2.4e-63	223.9
112	laminin_G	Laminin G domain	2.4e-03	-2.4
114	LBP_BPI_CETP	LBP / BPI / CETP family	1.1e-14	62.2
116	efhand	EF hand	4.8e-12	53.5
118	SAP	SAP domain		57.5
121	ig	Immunoglobulin domain	2.9e-16 1.7e-64	227.7
129	zf-C2H2	Zinc finger, C2H2 type		22.3
139	HSF_DNA-bind	HSF-type DNA-binding domain	1.7e-05	
140	7tm_1	7 transmembrane receptor (rhodopsin family)	1.1e-15	52.0
141	+;	Immunoglobulin domain	9.4e-09	33.3
	ig MHC II beta	Class II histocompatibility antigen,	2.7e-29	110.7
145	MHC_II_beta	beta		1

<del>=</del>	PFAM NAME	DESCRIPTION	p-value	PFAM
	PFAINI NAINIE	DESCIAI HON	P	SCORE
D				
NO:	<u>Cl.</u> : C	Fibrinogen beta and gamma chains,	1.3e-35	125.6
146	fibrinogen_C	C-term		
	•	Immunoglobulin domain	6.7e-05	20.8
154	ig	Immunoglobulin domain	0.00022	19.2
155	ig	Immunoglobulin domain	7e-19	65.9
158	ig	Immunogioouiii domain	3.5e-28	95.9
159	ig	Immunoglobulin domain	2.4e-06	25.5
160	ig	Immunoglobulin domain	1e-199	676.9
162	3Beta_HSD	3-beta hydroxysteroid	16-199	070.9
		dehydrogenase/isomera	2.1e-09	35.3
164	ig	Immunoglobulin domain	8.9e-141	481.1
169	p450	Cytochrome P450		450.0
170	p450	Cytochrome P450	2.1e-131	1
171	p450	Cytochrome P450	1.7e-112	387.1
173	FKBP	FKBP-type peptidyl-prolyl cis-trans	5.1e-27	89.2
		isomeras		1.50 -
174	sugar_tr	Sugar (and other) transporter	0.014	-120.6
187	CUB	CUB domain	2.2e-56	200.7
189	Apolipoprotein	Apolipoprotein A1/A4/E family	1.6e-06	34.6
191	ig	Immunoglobulin domain	1.7e-24	84.0
192	SPRY	SPRY domain	6.2e-13	56.4
193	fer4	4Fe-4S binding domain	1.6e-13	58.4
199	ank	Ank repeat	2.7e-09	44.3
209	zf-DHHC	DHHC zinc finger domain	4.6e-24	93.4
210	ATPIGI_PLM_MAT8		9.3e-22	85.7
211	Kelch	Kelch motif	0.02	20.8
212	DEAD	DEAD/DEAH box helicase	2.8e-52	168.3
213	DEAD	DEAD/DEAH box helicase	2.8e-52	168.3
214	Kunitz BPTI	Kunitz/Bovine pancreatic trypsin	3.7e-47	148.6
214	Kunte_Bi ii	inhibito		l
215	Acyltransferase	Acyltransferase	0.0023	4.4
216		Immunoglobulin domain	1.7e-10	38.9
	ig	Immunoglobulin domain	1.1e-08	33.1
217	ig	Spectrin repeat	0	1209.7
218	spectrin PH	PH domain	5.3e-08	33.6
219		Transmembrane amino acid	1.5e-21	85.0
220	Aa_trans	transporter protein		
202	-C0211C4	Zinc finger, C3HC4 type (RING	7.7e-07	26.4
223	zf-C3HC4		1 0	
	15.	finger)	0.00022	28.0
224	PA	PA domain	5.6e-13	56.6
227	kazal	Kazal-type serine protease inhibitor	3.06-13	30.0
		domain	4.7e-45	163.1
235	TBC	TBC domain	14.76-43	103.1

TABLE 5

SEQ ID NO:	POSITION OF SIGNAL IN AMINO ACID SEQUENCE	MaxS (MAXIMUM SCORE)	MeanS (MEAN SCORE)
1	1-16	0.907	0.635
2	1-45	0.970	0.723
3	1-31	0.970	0.770
4	1-25	0.929	0.655
5	1-28	0.990	0.860
6	1-18	0.977	0.916
7	1-22	0.990	0.921
8	1-45	0.973	0.605
9	1-22	0.991	0.915
10	1-18	0.910	0.637
11	1-20	0.997	0.915
12	1-21	0.967	0.949
13	1-22	0.985	0.949
14	1-29	0.932	0.690
15	1-15	0.933	0.831
16	1-19	0.985	0.932
17	1-21	0.996	0.951
18	1-18	0.942	0.764
19	1-18	0.954	0.725
20	1-29	0.891	0.625
21	1-31	0.992	0.895
22	1-18	0.974	0.820
23	1-16	0.994	0.917
24	1-32	0.983	0.865
26	1-22	0.975	0.874
27	1-19	0.943	0.723
28	1-21	0.971	0.925
30	1-31	0.970	0.770
31	1-26	0.958	0.844
32	1-19	0.959	0.930
34	1-41	0.958	0.553
	1-11	0.888	0.610
35	1-29	0.888	0.611
36	1-32	0.917	0.567
38	1-32	0.978	0.895
39		0.929	0.655
40	1-25	0.972	0.946
44	1-21	0.972	0.806
46	1-28		0.892
47	1-19	0.985	0.892
48	1-19	0.981	0.675
49	1-21	0.977	0.920
52	1-23	0.976	0.920
53	1-19	0.988	
55	1-15	0.901	0.782 0.772
58	1-24	0.953	
59	1-32	0.992	0.943

SEQ ID NO:	POSITION OF SIGNAL IN AMINO ACID SEQUENCE	MaxS (MAXIMUM SCORE)	MeanS (MEAN SCORE)
61	1-19	0.896	0.566
52	1-37	0.915	0.693
66	1-22	0.978	0.889
57	1-24	0.922	0.563
68	1-18	0.962	0.763
69	1-31	0.990	0.773
70	1-21	0.902	0.802
70 71	1-31	0.922	0.604
72	1-22	0.932	0.645
74	1-32	0.947	0.669
75	1-20	0.973	0.832
<del>73</del> 76	1-24	0.933	0.597
<del>70</del> 77	1-42	0.964	0.719
79	1-45	0.973	0.605
82	1-18	0.975	0.870
83	1-25	0.990	0.919
85	1-18	0.946	0.753
87	1-20	0.976	0.854
89	1-27	0.990	0.907
90	1-23	0.890	0.717
92	1-40	0.881	0.660
93	1-36	0.886	0.568
95	1-41	0.994	0.804
96	1-19	0.975	0.901
97	1-19	0.975	0.901
98	1-19	0.975	0.901
99	1-19	0.975	0.901
100	1-18	0.990	0.955
101	1-36	0.998	0.907
102	1-22	0.932	0.756
103	1-15	0.928	0.793
104	1-45	0.992	0.911
105	1-20	0.988	0.926
107	1-19	0.985	0.892
109	1-15	0.983	0.953
110	1-16	0.969	0.894
113	1-19	0.941	0.828
114	1-20	0.989	0.973
115	1-23	0.960	0.786
117	1-22	0.886	0.663
119	1-18	0.960	0.820
120	1-16	0.924	0.582
121	1-16	0.987	0.929
122	1-22	0.992	0.956
123	1-23	0.929	0.588
126	1-41	0.968	0.792
127	1-34	0.930	0.665

SEQ ID NO:	POSITION OF SIGNAL IN AMINO	MaxS (MAXIMUM SCORE)	MeanS (MEAN SCORE)
	ACID SEQUENCE	, 55514	,
128	1-42	0.957	0.653
130	1-21	0.897	0.632
131	1-25	0.983	0.845
132	1-13	0.947	0.915
133	1-13	0.930	0.824
134	1-22	0.947	0.857
135	1-25	0.978	0.936
137	1-17	0.960	0.878
141	1-16	0.983	0.952
142	1-23	0.945	0.798
145	1-29	0.979	0.884
146	1-25	0.922	0.765
147	1-37	0.928	0.786
148	1-28	0.981	0.890
150	1-20	0.986	0.965
151	1-20	0.987	0.886
152	1-18	0.922	0.809
153	1-19	0.887	0.607
154	1-16	0.964	0.790
155	1-17	0.984	0.973
156	1-21	0.929	0.692
157	1-21	0.937	0.836
158	1-19	0.897	0.722
159	1-19	0.985	0.932
160	1-21	0.978	0.833
161	1-20	0.940	0.632
165	1-20	0.954	0.696
167	1-20	0.988	0.963
168	1-20	0.986	0.952
169	1-8	0.983	0.634
170	1-8	0.983	0.634
171	1-40	0.994	0.888
173	1-27	0.982	0.925
174	1-17	0.989	0.945
176	1-21	0.987	0.919
177	1-21	0.950	0.596
178	1-22	0.986	0.949
179	1-18	0.942	0.764
181	1-16	0.917	0.618
182	1-23	0.963	0.889
183	1-25	0.992	0.968
184	1-19	0.945	0.638
185	1-31	0.964	0.709
186	1-37	0.978	0.830
187	1-27	0.947	0.799
190	1-41	0.972	0.836
193	1-16	0.900	0.664

SEQ ID NO:	POSITION OF	MaxS (MAXIMUM	MeanS (MEAN
	SIGNAL IN AMINO	SCORE)	SCORE)
	ACID SEQUENCE		
194	1-35	0.988	0.912
195	1-16	0.944	0.837
196	1-28	0.925	0.626
197	1-20	0.962	0.811
198	1-21	0.947	0.701
199	1-20	0.945	0.854
200	1-34	0.967	0.718
201	1-32	0.994	0.956
203	1-18	0.953	0.786
204	1-24	0.968	0.728
205	1-32	0.920	0.623
206	1-27	0.974	0.843
208	1-31	0.986	0.878
209	1-29	0.997	0.854
214	1-19	0.986	0.967
215	1-37	0.981	0.952
216	1-18	0.974	0.820
217	1-18	0.974	0.820
218	1-21	0.937	0.819
219	1-31	0.914	0.554
224	1-21	0.981	0.945
225	1-25	0.938	0.890
227	1-22	0.965	0.891
230	1-23	0.884	0.746
231	1-14	0.885	0.675
232	1-20	0.930	0.729

TABLE 6

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
1	237	473	709	785CIP2B_1	10
2	238	474	710	785CIP2B_2	449
3	239	475	711	785CIP2B_3	1376
4	240	476	712	785CIP2B_4	1425
5	241	477	713	785CIP2B_5	1472
6	242	478	714	785CIP2B_6	1503
7	243	479	715	785CIP2B_7	1513
8	244	480	716	785CIP2B_8	1518
9	245	481	717	785CIP2B_9	1525
10	246	482	718	785CIP2B_10	1533
11	247	483	719	785CIP2B_11	1537
12	248	484	720	785CIP2B_12	1542
13	249	485	721	785CIP2B_13	1549
14	250	486	722	785CIP2B_14	1560
15	251	487	723	785CIP2B 15	1715
16	252	488	724	785CIP2B 16	1731
17	253	489	725	785CIP2B 17	1757
18	254	490	726	785CIP2B 18	1791
19	255	491	727	785CIP2B 19	1809
20	256	492	728	785CIP2B 20	1818
21	257	493	729	785CIP2B 21	1857
22	258	494	730	785CIP2B_22	1869
23	259	495	731	785CIP2B 23	1905
24	260	496	732	785CIP2B_24	1910
25	261	497	733	785CIP2B_25	1917
26	262	498	734	785CIP2B_26	1924
27	263	499	735	785CIP2B_27	1937
28	264	500	736	785CIP2B 28	1965
29	265	501	737	785CIP2B_29	2033
30	266	502	738	785CIP2B_30	2035
31	267	503	739	785CIP2B_31	2194
32	268	504	740	785CIP2B_32	2195
33	269	505	741	785CIP2B_33	2197
34	270	506	742	785CIP2B_34	2199
35	271	507	743	785CIP2B 35	2201
36	272	508	744	785CIP2B 36	2201
37	273	509	745	785CIP2B 37	2253
38	274	510	746	785CIP2B 38	2257
39	275	511	747	785CIP2B 39	2264
40	276	512	748	785CIP2B 40	2264
41	277	513	749	785CIP2B 41	2266
42	278	514	750	785CIP2B 42	2272
43	279	515	751	785CIP2B 43	2272
44	280	516	752	785CIP2B 44	2274
L	200	1310	1.52		1

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
ength	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		1
45	281	517	753	785CIP2B 45	2283
46	282	518	754	785CIP2B 46	2285
47	283	519	755	785CIP2B 47	2289
48	284	520	756	785CIP2B 48	2294
49	285	521	757	785CIP2B 49	2295
50	286	522	758	785CIP2B 50	2297
51	287	523	759	785CIP2B 51	2301
52	288	524	760	785CIP2B 52	2312
53	289	525	761	785CIP2B 53	2313
54	290	526	762	785CIP2B 54	2324
55	291	527	763	785CIP2B 55	2337
56	292	528	764	785CIP2B 56	2338
57	293	529	765	785CIP2B 57	2345
58	294	530	766	785CIP2B 58	2359
59	295	531	767	785CIP2B 59	2361
60	296	532	768	785CIP2B 60	2369
61	297	533	769	785CIP2B 61	2379
62	298	534	770	785CIP2B 62	2382
63	299	535	771	785CIP2B 63	2389
64	300	536	772	785CIP2B 65	2400
65	301	537	773	785CIP2B 66	2411
66	301	538	774	785CIP2B 67	2422
67	302	539	775	785CIP2B 68	2425
68	304	540	776	785CIP2B 69	2426
69	305	541	777	785CIP2B 70	2428
	306	542	778	785CIP2B 71	2431
70 71	307	543	779	785CIP2B 72	2440
72	308	544	780	785CIP2B 73	2443
73	309	545	781	785CIP2B 74	2451
74	310	546	782	785CIP2B 75	2458
75	311	547	783	785CIP2B_76	2462
76	312	548	784	785CIP2B 77	2470
		549	785	785CIP2B 78	2487
77	313	550	786	785CIP2B 79	2497
78 79		551	787	785CIP2B 80	2504
80	315	552	788	785CIP2B 81	2510
81	317	553	789	785CIP2B 82	2513
82	317	554	790	785CIP2B 83	2519
		555	790	785CIP2B 84	2520
83	319	556	791	785CIP2B_85	2524
84		I	793	785CIP2B_86	2528
85	321	557	794	785CIP2B_80	2531
86	322	558	794	785CIP2B_87	2558
87	323	559	l	785CIP2B_88	2567
88	324	560	796 797	785CIP2B_89 785CIP2B_90	2584
	325	561	1/9/	1 /83CIPZB 90	12304

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence	1	
91	327	563	799	785CIP2B 92	2594
92	328	564	800	785CIP2B 93	2596
93	329	565	801	785CIP2B 94	2599
94	330	566	802	785CIP2B 95	2601
95	331	567	803	785CIP2B 96	2603
96	332	568	804	785CIP2B 97	2604
97	333	569	805	785CIP2B 98	2604
98	334	570	806	785CIP2B 99	2604
99	335	571	807	785CIP2B 100	2604
100	336	572	808	785CIP2B 101	2610
101	337	573	809	785CIP2B 102	2612
102	338	574	810	785CIP2B 103	2626
103	339	575	811	785CIP2B 104	2629
104	340	576	812	785CIP2B 105	2630
105	341	577	813	785CIP2B 106	2631
106	342	578	814	785CIP2B 107	2639
107	343	579	815	785CIP2B 108	2651
108	344	580	816	785CIP2B 109	2652
109	345	581	817	785CIP2B 110	2661
110	346	582	818	785CIP2B 111	2662
111	347	583	819	785CIP2B 112	2677
112	348	584	820	785CIP2B 113	2677
113	349	585	821	785CIP2B 114	2680
114	350	586	822	785CIP2B 115	2688
115	351	587	823	785CIP2B 116	2693
116	352	588	824	785CIP2B 117	2716
117	353	589	825	785CIP2B 118	2720
118	354	590	826	785CIP2B 119	2721
119	355	591	827	785CIP2B 120	2724
120	356	592	828	785CIP2B 121	2725
121	357	593	829	785CIP2B 122	2727
122	358	594	830	785CIP2B 123	2739
123	359	595	831	785CIP2B 124	2740
124	360	596	832	785CIP2B 125	2747
125	361	597	833	785CIP2B 126	2748
126	362	598	834	785CIP2B 127	2752
127	363	599	835	785CIP2B 128	2755
128	364	600	836	785CIP2B_129	2764
129	365	601	837	785CIP2B 130	2773
130	366	602	838	785CIP2B 131	2778
131	367	603	839	785CIP2B_131	2779
132	368	604	840	785CIP2B_132 785CIP2B_133	2780
133	369	605	841	785CIP2B_133	2780
134	370	606	842	785CIP2B_134 785CIP2B_135	2786
135	370	607	843	785CIP2B_133	2790
136	372	608	844	785CIP2B_136 785CIP2B_137	2790
130	312	000	044	/83CIFZB_13/	2/91

WO 01	133437		_		
SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
ength	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
137	373	609	845	785CIP2B_138	2795
138	374	610	846	785CIP2B_139	2801
139	375	611	847	785CIP2B_140	2802
140	376	612	848	785CIP2B_141	2804
141	377	613	849	785CIP2B_142	2811
142	378	614	850	785CIP2B_143	2820
143	379	615	851	785CIP2B_144	2825
144	380	616	852	785CIP2B_145	2836
145	381	617	853	785CIP2B_146	2841
146	382	618	854	785CIP2B_147	2843
147	383	619	855	785CIP2B_148	2844
148	384	620	856	785CIP2B_149	2845
149	385	621	857	785CIP2B_150	2849
150	386	622	858	785CIP2B_151	2850
151	387	623	859	785CIP2B_152	2866
152	388	624	860	785CIP2B_153	2873
153	389	625	861	785CIP2B_154	2874
154	390	626	862	785CIP2B_155	2878
155	391	627	863	785CIP2B_156	2882
156	392	628	864	785CIP2B_157	2888
157	393	629	865	785CIP2B_158	2894
158	394	630	866	785CIP2B_159	2899
159	395	631	867	785CIP2B 160	2899
160	396	632	868	785CIP2B 161	2903
161	397	633	869	785CIP2B_162	2905
162	398	634	870	785CIP2B 163	2913
163	399	635	871	785CIP2B 164	2920
164	400	636	872	785CIP2B 165	2927
165	401	637	873	785CIP2B 166	2938
166	402	638	874	785CIP2B 167	2952
167	403	639	875	785CIP2B 168	2954
168	404	640	876	785CIP2B 169	2954
169	405	641	877	785CIP2B 170	2958
170	406	642	878	785CIP2B 171	2958
171	407	643	879	785CIP2B 172	2958
172	408	644	880	785CIP2B 173	2959
173	409	645	881	785CIP2B 174	2961
174	410	646	882	785CIP2B 175	2978
175	411	647	883	785CIP2B 176	2981
176	412	648	884	785CIP2B 177	2996
177	413	649	885	785CIP2B 178	2997
178	414	650	886	785CIP2B 179	3001
178	415	651	887	785CIP2B 180	3006
180	416	652	888	785CIP2B 181	3007
	417	653	889	785CIP2B 182	3010
181	417	654	890	785CIP2B 183	3034

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
183	419	655	891	785CIP2B 184	3058
184	420	656	892	785CIP2B 185	3060
185	421	657	893	785CIP2B 186	3061
186	422	658	894	785CIP2B 187	3078
187	423	659	895	785CIP2B 188	3081
188	424	660	896	785CIP2B 189	3083
189	425	661	897	785CIP2B 190	3086
190	426	662	898	785CIP2B 191	3090
191	427	663	899	785CIP2B 193	3102
192	428	664	900	785CIP2B 194	3110
193	429	665	901	785CIP2B 195	3117
194	430	666	902	785CIP2B 196	3118
195	431	667	903	785CIP2B 197	3121
196	432	668	904	785CIP2B 198	3124
197	433	669	905	785CIP2B 199	3131
198	434	670	906	785CIP2B 200	3132
199	435	671	907	785CIP2B 201	3135
200	436	672	908	785CIP2B 202	3143
201	437	673	909	785CIP2B 203	3145
202	438	674	910	785CIP2B 204	3156
203	439	675	911	785CIP2B 205	3160
204	440	676	912	785CIP2B 206	3163
205	441	677	913	785CIP2B 207	3167
206	442	678	914	785CIP2B 208	3170
207	443	679	915	785CIP2B 209	3174
208	444	680	916	785CIP2B 210	3176
209	445	681	917	785CIP2B 211	3178
210	446	682	918	785CIP2B 212	3180
211	447	683	919	785CIP2B 213	3791
212	448	684	920	785CIP2B 215	3793
213	449	685	921	785CIP2B 216	3793
214	450	686	922	785CIP2B 217	3794
215	451	687	923	785CIP2B 218	3795
216	452	688	924	785CIP2B 219	3796
217	453	689	925	785CIP2B 220	3796
218	454	690	926	785CIP2C_1	145
219	455	691	927	785CIP2C 3	639
220	456	692	928	785CIP2C 4	652
221	457	693	929	785CIP2C 5	753
222	458	694	930	785CIP2C 6	754
223	459	695	931	785CIP2C 7	1258
224	460	696	932	785CIP2C 8	1316
225	461	697	933	785CIP2C 9	1343
226	462	698	934	785CIP2C 11	1499
227	463	699	935	785CIP2C 12	1659
228	464	700	936	785CIP2C_12	2024
220	דטד	L,00	730	103CIF2C_13	2024

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
229	465	701	937	785CIP2C_15	2114
230	466	702	938	785CIP2C_16	2119
231	467	703	939	785CIP2C_17	2126
232	468	704	940	785CIP2C_19	2137
233	469	705	941	785CIP2C_20	2143
234	470	706	942	785CIP2C_21	2145
235	471	707	943	785CIP2C_22	2853
236	472	708	944	785CIP2C_24	3076

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## TABLE 7

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
709	465	301	MGKSLASQFPITLIFSAFSSTFCLLDGLFISCPCT
			STELPKVNSLLSRPESATT*
710	1181	1345	MLALSSSFLVLSYLLTRWCGSVGFILANCFNM
			GIRITQSLCFIHRYYRRSPHRPL
711	186	701	MKVLWAALLVTFLAGCQAKVEQAVETEPEPE
ŀ			LRQQTEWQSGQRWELALGRFWDYLRWVQTLS
			EQVQEELLSSQVTQELRALMDETMKELKAYKS
			ELEEQLTPVAEETRARLSKELQAAQARLGADM
			EDVCGRLGAVTAVMVQGHARPEQPRSCGWRV
			RLPPAQAGVSGSLR*
712	3917	4081	MFRRLTFAQLLFATVLGIAGGVYIFQPVFEQYA
			KDQKELKEKMQLVQESEEKKS*
713	26	1123	MSLLGFLLSRLGLLLKVLLDWPVEVLYGAAAL
			NGLFGGFSAFWSGVMALGSLGSSEGRRSVRLIL
			IDLMLGLAGFCGSMASGHLFKQMAGHSGQGLI
			LTACSVSCASFALLYSLLVLKVPESVAKPSQEL
			PAVDTVSGTVGTYRTLDPDQLDQQYAVGHPPS
			PGKAKPHKTTIALLFVGAIIYDLAVVGTVDVIPL
1			FVLREPLGWNQVQVGYGMAAGYTIFITSFLGV
			LVFSRCFRDTTMIMIGMVSFGSGALLLAFVKET
			YMFYIARAVMLFALIPVTTIRSAMSKLIKGSSY
			GKVFVILQLSLALTGVVTSTLYNKIYQLTMDM FGGSCFALSSFLSFLAIIPISIVAYKQVPLSPYGDI
			IEK*
714	39	431	MFLFLFFLVAILPVNTEGGEIIWGTESKPHSRPY
/14		171	MAFIKFYDSNSEPHHCGGFLVAKDIVMTAAHC
			NGRNIKVTLGAHNIKKQENTQVISVVKAKPHE
			NYDRDSHFNDIMLLKLERKAQLNGCCEDYCPS
			*
715	970	1755	MLVLLVLRVSLAALVKMELLVRWAPVACLVR
			EVALEPLALLVLVEMMVLLVLPGPLVPPAPLV
			LLASLVLLVLRVKLVPKGPEALKVPRVCVVSL
			APLALLVLLALLETLVLRESLVLKVPMVLLVLL
			VLLASLVPEAPLDPRAPAALLVPRVTAVNLVLL
			AAKETLVLRESLALLVFKDPLALLERKESEELE
			VNPDPLACPDPLASVVDLVAVVSLAQMVLLVP
			RVPLVNVVLLALLAPKDLLVKLVVPVKLVCLV
			PRV*
716	3060	2899	MMLLVSLHILFPFMPFSYGLESNNSKPQCLMKL
			TLQNLQKQVAFEVFSHTKYN*
717	70	618	MGWTMRLVTAALLLGLMMVVTGDEDENSPC

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	1	1
	1	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino acid residue of	M=Methionine, N=Asparagine, P=Proline,
	to first amino		Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			AHEALLDEDTLFCQGLEVFYPELGNIGCKVVPD
			CNNYRQKITSWMEPIVKFPGAVDGATYILVMV
		·	DPDAPSRAEPRQRFWRHWLVTDIKGADLKEGK
			IQGQELSALPGSLPHRHTVAFHRYQVLCLSSGR
			EKSSLSFPRKTKLEALGKWTDF*
718	79	342	MRRSFWTVMRTAWRCSCSSVDRALSHQAGLQ
	1		GQCLSACLLGNLGYPPFISPPAQVLCAARASCH
			LGSLMAHFETLVHSKDWSCVILK*
719	382	1326	MLFWVLGLLILCGFLWTRKGKLKIEDITDKYIFI
			TGCDSGFGNLAARTFDKKGFHVIAACLTESGST
			ALKAETSERLRTVLLDVTDPENVKRTAQWVK
		·	NQVGEKGLWGLINNAGVPGVLAPTDWLTLED
			YREPIEVNLFGLISVTLNMLPLVKKAQGRVINV
			SSVGGRLAIVGGGYTPSKYAVEGFNDSLRRDM
			KAFGVHVSCIEPGLFKTNLADPVKVIEKKLAIW
			EQLSPDIKQQYGEGYIEKSLDKLKGNKSYVNM
			DLSPVVECMDHALTSLFPKTHYAAGKDAKIFW
			IPLSHMPAALQDFLLLKQKARAG*
720	875	516	MSVPTMAWMMLLLGLLAYGSGVESQTVVTQE
			PSLSVSPGGTVTLTCGLTSGSVSTSFYPSWYQQ
			TPGQAPRTLIYSTNTRSSGVPGRFSGSILGSKAA
			LTITGAQADDESDYYCVLICR*
721	431	3643	MNCDVLWCVLLLVCMSLFSAVGHGLWIWRY
			QEKKSLFYVPKSDGSSLSPVTAAVYSFLTMIIVL
			QVLIPISLYVSIEIVKACQVYFINQDMQLYDEET
			DSQLQCRALNITEDLGQIQYIFSDKTGTLTENK
		<u> </u>	MVFRRCTVSGVEYSHDANAQRLARYQEADSE
			EEEVVPRGGSVSQRGSIGSHQSVRVVHRTQSTK
			SHRRTGSRAEAKRASMLSKHTAFSSPMEKDITP
			DPKLLEKVSECDKSLAVARHQEHLLAHLSPELS
			DVFDFLIALTICNTVVVTSPDQPRTKVRVRFEL
			KSPVKTIEDFLRRFTPSCLTSGCSSIGSLAANKSS
			HKLGSSFPSTPSSDGMLLRLEERLGQPTSAIASN
			GYSSQADNWASELAQEQESERELRYEAESPDE
			AALVYAARAYNCVLVERLHDQVSVELPHLGR
			LTFELLHTLGFDSVRKRMSVVIRHPLTDEINVY
		1	TKGADSVVMDLLQPCSSVDARGRHQKKIRSKT
			QNYLNVYAAEGLRTLCIAKRVLSKEEYACWLQ
			SHLEAESSLENSEELLFQSAIRLETNLHLLGATG
			IEDRLQDGVPETISKLRQAGLQIWVLTGDKQET
			AVNIAYACKLLDHDEEVITLNATSQEACAALL
			DQCLCYVQSRGPQRAPEKTKGKVSMRFSSLCP
ŀ			PSTSTASGRRPSLVIDGRSMAYALEKNLEDKFL

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	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
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	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
1	sequence	sequence	deletion, \=possible nucleotide insertion
	1		FLAKQCRSVLCCRSTPLQKSMVVKLVRSKLKA
			MTLAIGDGANDVSMIQVADVGVGISGQEGMQ
			AVMASDFAVPKFRYLERLLILHGHWCYSRLAN
			MVLYFFYKNTMFVGLLFWFQFFCGFSASTMID
			QWYLIFFNLLFSSLPPLVTGVLDRDVPANVLLT
			NPQLYKSGQNMEEYRPRTFWFNMADAAFOSL
			VCFSIPYLAYYDSNVDLFTWGTPIVTIALLTFLL
			HLGIETKTWTWLNWITCGFSVLLFFTVALIYNA
			SCATCYPPSNPYWTMQALLGDPVFYLTCLMTP
			VAALLPRLFFRSLQGRVFPTQLQLARQLTRKSP
i			RRCSAPKETFAQGRPXEGLGNRGTHQGGQSRP
			LCPCPSLLGTHSSRSAPWRPAGSPAQWT*
722	3616	1673	MLWVTGPVLAVILIILIVIAILLFKRKRTHSPSSK
			DEQSIGLKDSLLAHSSDPVEMRRLNYQTPGMR
			DHPPIPITDLADNIERLKANDGLKFSQEYESIDP
			GQQFTWENSNLEVNKPKNRYANVIAYDHSRVI
			LTSIDGVPGSDYINANYIDGYRKQNAYIATQGP
			LPETMGDFWRMVWEQRTATVVMMTRLEEKS
			RVKCDQYWPARGTETCGLIQVTLLDTVELATY
ļ			TVRTFALHKSGSSEKRELRQFQFMAWPDHGVP
•			EYPTPILAFLRRVKACNPLDAGPMVVHCSAGV
			GRTGCFIVIDAMLERMKHEKTVDIYGHVTCMR
			SQRNYMVQTEDQYVFIHEALLEAATCGHTEVP
}			ARNLYAHIQKLGQVPPGESVTAMELEFKLLASS
			KAHTSRFISANLPCNKFKNRLVNIMPYELTRVC
			LQPIRGVEGSDYINASFLDGYRQQKAYIATQGP
			LAESTEDFWRMLWEHNSTIIVMLTKLREMGRE
			KCHQYWPAERSARYQYFVVDPMAEYNMPQYI
			LREFKVTDARDGQSRTIRQFQFTDWPEQGVPK
			TGEGFIDFIGQVHKTKEQFGQDGPITVHCSAGV
	ļ		GRTGVFITLSIVLERMRYEGVVDMFQTVKTLRT
			QRPAMVQTEDQYQLCYRAALEYLGSFDHYAT
			*
723	484	765	MIWIYFAFIFQRLHLIPGKSSARQVSGFSLLSFNP
		j	SNTIFVKLDWWCFIQLIYSAYLFEKRLLEIDDVF
			VPVILKVVGARIEFHSGIGFGSGL*
724	846	983	MLIAVIACICYLSLLHSYDILFGHFSVLSQGLDK
			HCLTLFLSLGG*
725	154	513	MVIINCSPRFWFLFPFTIQHTCKCPLGVRYHTRH
			LEQIAANKKHCPYPYEVHYNSSYWRAGIILHTL
			HAYLTSYPHYYSFFFFFGKGVPFCPQGGGAGK
<b>7</b> 0 :			GSGLMGSHRGTKPKSFLKKK
726	709	566	MERHGFFLDVCLILGLIPLSIKYSLQKRGKNSA

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	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	1	V-Vallie, W-Hyptophan, 1=1 yrosine,
	sequence	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
<del></del>	sequence		deletion, \=possible nucleotide insertion
727	175	242	ADNAGWSDLSLGQN*
121	1/3	342	MYMNTCLYLHVYVLTCSGCNVDMCSRLFLST
728	109	264	KLKAHVQIVLYWVFLWSRGNNFLT*
128	109	264	MVILDVLELYHMWFLGILYDAIFYCFVHAINA
720	66		DKFFGLKLTKSATVSQNSQ*
729	56	220	MYDFLLLLSFIFIVASYWSFLSTIFLDVVCSILHC
730	50.5		PVKPQTLLKSCLHVDCKST*
/30	735	1235	MVGLGGMSQLLLASLLPPVPQGSPTRRKLPASL
			LVSTALISPVCVRGWMWQNLQNRIHGSHTSAR
		<u>,</u>	RVPSLPGAGQVGVRWEAGPACRTQPSPQNLAP
			RPHPSAAQLIENAALRSAMSGERLFPEGQEHLG
			PLVAPRVPMGGALCPPLPSLSCAICKVGAAREA
<b>#</b> 2.1	100		GGR*
731	109	303	MKPYCMYPFLSGLLSSLLFWVESLMLLCVQMV
700			LFLMLCVLDYRIYCIKIYVSIILLMSIWIISI*
732	165	359	MCYFYNTIILTLQGSLMFLLFSVVTLYLFSHSHP
			TPISIFSDVFNMYPWIYMYSYMVFSVNLYK*
733	7	279	MAAAPGLLVWLLVLRLPWRVPGQLDPSTGRR
			FSEHKLCADDECSMLMYRGEALEDFTGPDCRF
70.1			VNFKKGDPVYVYYKLARGWPEVWAGSK*
734	81	275	MPGYVPLLLLLLLRCSQRGGGVNFGEKDAKV
	· ·		PGTWRDGVRVPGEGASWDSDRASPERRYGIGE
			*
735	207	419	MKFLLMSLPYRHLFCITQAILSEIAEGIRNDPFK
			FYLYSVLALFLHYYMYVFVSRFSIYYLKLLRIF
			KFS*
736	233	457	MRQIAVFQRFMFPFLLPWLSCIFSSSQNSIYYVS
		•	TFIKCLALKSIIKRQRSEINSGFLAIYHALRNQVT
			RCGGL*
737	39	251	MPRRTRGGLWLCNAHKSCQKYLSSLKLSTLLS
			PLLVLPFYTPSLKGWGIFVLRFYFMVIIADCNLF
			KIII*
738	155	313	MFTHWLGPPVYIKQFIVMIVSILTLFPVLQGML
			RNFLYLNIMFVVALLKAIL*
739	60	272	MERGAGAKLLPLLLLRATGFTCAQADGRNG
			YTAVIEVTSGGPWGDWAWPEMCPDGFFASGFS
			LKVGAQA*
740	49	360	MTQVERVIVFLTLSTLSLAKTTQPIFMDSYEGQ
ł			EVNITCSHNNIVTNDYITWYQQFPSQGPRFIIQG
İ			YQKKVTNEVAFLCIPADRKSITLNLPRVSLEDT
			GGK*
741	47	325	MTKLAQWLWGLAILGSTWVALTTGALGLELP
			LSCQEVLWPLPAYLLVSAGCYALGTVGYRVAT
	<del></del>		, -= -=

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	
	acid residue	1	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
		amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			FHDCEDAARELQSQIQEARADLARRGLRF*
742	301	438	MSVGLAGAVGRRCHLALAVLHDPLCHHGSLA
742	175	412	TICKQPEVCLFTIV*
743	165	413	MPFLLNQCGSLLYYLTLASTDLTLAVPICNSLAI
			IFTLIVGKALGEDIGGKRAVAGMVLTVIGISLCI
			TSSVSKTQGQQSTL*
744	165	413	MPFLLNQCGSLLYYLTLASTDLTLAVPICNSLAI
	ļ		IFTLIVGKALGEDIGGKRAVAGMVLTVIGISLCI
			TSSVSKTQGQQSTL*
745	923	1618	MALIYVMLLLLGAFLGAWPALCGRYKRWRKH
			GVFVLLTTATSVAIWVVWIVMYTYGNKQHNS
			PTWDDPTLAIALAANAWAFVLFYVIPEVSQVT
			KSSPEQSYQGDMYPTRGVGYETILKEQKGQSM
			FVENKAFSMDEPVAAKRPVSPYSGYNGQLLTS
			VYQPTEMALMHKVPSEGAYDIILPRATANSQV
			MGSANSTLRAEDMYSAQSHQAATPPKDGKNS
			QVFRNPYVWD*
746	14	370	MVKTDAHLKNPPFAPFRVYTLTLSLLLKLSHYS
			CLWVKKDFKDSSFYNSNNNSNSNHCKSLLSTH
}			YMPGAVISNLCLISCKVSSSPIKQTHGISMLQM
			KRLKHTLARLAPGTHGGSQN*
747	103	1002	MGTKAQVERKLLCLFILAILLCSLALGSVTVHS
			SEPEVRIPENNPVKLSCAYSGFSSPRVEWKFDQ
			GDTTRLVCYNNKITASYEDRVTFLPTGITFKSV
			TREDTGTYTCMVSEEGGNSYGEVKVKLIVLVP
			PSKPTVNIPSSATIGNRAVLTCSEQDGSPPSEYT
			WFKDGIVMPTNPKSTRAFSNSSYVLNPTTGELV
			FDPLSASDTGEYSCEARNGYGTPMTSNAVRME
			AVERNVGVIVAAVLVTLILLGILVFGIWFAYSR
			GHFDRTKKGTSSKKVIYSQPSARSEGEFKQTSS
			FLV*
748	103	1002	MGTKAQVERKLLCLFILAILLCSLALGSVTVHS
			SEPEVRIPENNPVKLSCAYSGFSSPRVEWKFDQ
			GDTTRLVCYNNKITASYEDRVTFLPTGITFKSV
		ļ	TREDTGTYTCMVSEEGGNSYGEVKVKLIVLVP
			PSKPTVNIPSSATIGNRAVLTCSEQDGSPPSEYT
			WFKDGIVMPTNPKSTRAFSNSSYVLNPTTGELV
			FDPLSASDTGEYSCEARNGYGTPMTSNAVRME
			AVERNVGVIVAAVLVTLILLGILVFGIWFAYSR
			GHFDRTKKGTSSKKVIYSQPSARSEGEFKQTSS
			FLV*
749	970	1263	MPSSFFLLLRFFLRIDGVLIRMNDTRLYHEADK
			TYMLREYTSRESKISSLMHVPPSLFTEPNEISQY

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NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	Li-Uistiding I-Isalassias K. I
	1	to first amino	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
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		acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
1	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
	100		LPIKEAVCEKLIFPERIDPNPADSQKSTQVE
750	1207	887	MYTRELLAWIQGLYTWELLAWIQHLNTWELL
			PWIRRLNSWILLVCPKLLHLWVFGKTMEIFVLV
			KDMMPFLYKKELCLVPEVISLLIFSHLDTSKELS
			IYGLTQLI*
751	1207	887	MYTRELLAWIQGLYTWELLAWIQHLNTWELL
		·	PWIRRLNSWILLVCPKLLHLWVFGKTMEIFVLV
			KDMMPFLYKKELCLVPEVISLLIFSHLDTSKELS
		L	IYGLTQLI*
752	43	948	MFSHLPFDCVLLLLLLLTRSSEVEYRAEVGON
			AYLPCFYTPAAPGNLVPVCWGKGACPVFECGN
			VVLRTDERDVNYWTSRYWLNGDFRKGDVSLT
			IENVTLADSGIYCCRIQIPGIMNDEKFNLKLVIK
			PAKVTPAPTLQRDFTAAFPRMLTTRGHGPAET
			QTLGSLPDINLTQISTLANELRDSRLANDLRDSG
			ATIRIGIYIGAGICAGLALALIFGALIFKWYSHSK
1			EKIQNLSLISLANLPPSGLANAVAEGIRSEENIYT
			IEENVYEVEEPNEYYCYVSSRQQPSQPLGCRFA
			MP*
753	2350	2180	MGGVAFLLWLTVFSAWTRLSIFSRLSDLPSFCL
ľ		,	PLAGTVSSSLPEGSGCSFSSSTK*
754	369	707	MCHWQNSFLCQSFLTFGSILALLAGKACYPESE
			SIRELFMWALELYSLPFYLFFKLSPLNLPGKLGL
			IETLSTCWGQKLDPVLETLQRVRSMASLIANFF
			VPFIQKKGQLIT*
755	847	149	MAWIPLFLGVLAYCTGSVASYELTQPPSVSVSP
			GQTASITCSGDNLGNKYVAWYQQKAGQSPVL
			VIYQDDKRPSEIPERFSGSNSGNTATLTISGTQA
			MDEADYYCQAWDSSTAVMFGGGTKLTVLGQP
			KAAPSVTLFPPSSEELQANKATLVCLISDFYPGA
			VTVAWKADSSPVKAGVETTTPSKQSNNKYAA
			SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTV
			APTECS*
756	1726	1869	MGAGCTPVVLGAALWLWRWFSRWGLGGLCW
		2	RPCTCTPCHSASPGAGR*
757	167	310	MLGICLCSICVLRLCLEKSKIFPPPRTSDHSLEGS
	- 1	<del>-</del>	VTPVENAARSGM*
758	335	778	MSITRLFPALLECFVIVLCGYIAGRANVITSTQA
			KGLGNFVSRFALPALLFKNMVVLNFSNVDWAF
			LYSILIAKASVFFIVCVLTLLVASPDSRFSKAGLF
			PIFATQSNDFALGYPIGKLIFIFQVFKKFNFNLFR
			HLLVTDSYSHI*
759	102	419	MWLGQAFWAWLSFMNRWHSKFLMVRSRGEC
			THE ALM MAN TOLIMINK MUSKLTMAKSKOEC

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	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
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	sequence		GAQRQLLCVFVFRDSLREGMPRRNMVSSEAHG
			CLLRTAVFYATYPCTSYAKETKPSACLFPLLIIG
	l		KWMLWSFKN*
760	27	371	MSSWFLRAGHGLIWVLFFRIGQAAVGVSAGPG
700	21	371	GSPKAHLGRVASQHPHGAESRACLLARGLPKA
			LSSMLAVDCRPRSGPLHRAAHIMAASLISKPVR
			GCLSEDDIPSPLSDSAY*
561	400	685	
761	428	083	MGWDSKLLFLFTCLSCVTTCSVSTCFQAPLGSS
			SFAPSGIHGTLEFPVVRGAHKNFLPMGPMYLFP
260	003	<u> </u>	ITAGQPLTLFVKTQSAGRN*
762	293	3	MCHVHCCWKFIVELLQCVIQGIRCLYFGNICNG
			TCFLESCFFGMSFQGANFLFFGNSHSSSFYCRR
7.0		205	MSPFPRGEQVLHFICHSVCQCQCQCWCSGG*
763	38	385	MLLWVFLQLNYKIQAIPTYETVMTFFKSFPENC
			CFLDRDIGQSLRPLFLCLRLHGITKGKDXEVLR
			HLNFFPESWLDQVTVNHYHALENGGDMVHLK
			DLNTQAVRFGLLFNQENTT
764	508	1374	MLAMGALAGFWILCLLTYGYLSWGQALEEEE
			EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF
			RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP
			ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL
			DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC
			MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC
		į	GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI
			LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY
			RSIININRRRYAAMLSCLDEAINNVTLALK
765	660	875	MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF
			NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT
			YN*
766	316	456	MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF
			QLSFERRPKSVR*
767	231	584	MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV
			QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG
			CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA
			PCGSGIPKFSKCLSVS*
768	135	305	MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV
			KTYFPNSSSFYRATPMVLDFILH*
769	231	401	MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK
			PESQESFLSTIHLLEGAQEGTPTE*
770	141	314	MRETGILLCFLSALNYITLVTSQKLILSKKMHV
			NHYLPKKTISKFLYFVKVFHDLVL*
771	55	276	MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP
		•	SLFHLVCCADPLPWMPAHSFGSPFWSLFSTYPG
	L	l	

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	to first amino	acid residue of	
	acid residue	1	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
		amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
550			RNSRGCQ*
772	139	354	MLLFSLNFFFWKIVMFHKNVIFILTCNGFIIVTF
			KWIDKFILNISILISNTVNVNSHNPHKQKFFGDL
			SNF*
773	269	457	MQLKFSQLTTSSLSFSSALWLLAFSRVFLLADS
			NLFVKPSSDLGSDTCSADFCDFRKLSFFR*
774	96	1385	MCPGALWVALPLLSLLAGSLQGKPLQSWGRGS
	-		AGGNAHSPLGVPGGGLPEHTFNLKMFLENVKV
	<u> </u>		DFLRSLNLSGVPSQDKTRVEPPQYMIDLYNRYT
			SDKSTTPASNIVRSFSMEDAISITATEDFPFQKHI
			LLFNISIPRHEQITRAELRLYVSCQNHVDPSHDL
			KGSVVIYDVLDGTDAWDSATETKTFLVSQDIQ
			DEGWETLEVSSAVKRWVRSDSTKSKNKLEVT
		ļ	VESHRKGCDTLDISVPPGSRNLPFFVVFSNDHSS
			GTKETRLELREMISHEQESVLKKLSKDGSTEAG
1			ESSHEEDTDGHVAAGSTLARRKRSAGAGSHCO
			KTSLRVNFEDIGWDSWIIAPKEYEAYECKGGCF
}			FPLADDVTPTKHAIVQTLVHLKFPTKVGKACC
			VPTKLSPISVLYKDDMGVPTLKYHYEGMSVAE
			CGCR*
775	187	354	MFGMIKRRVRRAVFVGRTVLCGSCNSGIIMHR
			GKTPPLKMVCRFEESFSCLFLNS*
776	22	168	MGFLFLLDSALMQTWVTVIDVSLHHVEIKAPRI
		100	RLMWSLPLRRQKYTM*
777	37	357	MLATLACMAIPWTHLGCSCLLACLPFSHHLGL
' ' '	3,	337	
			SEDIISSEKPSVTMLSKILQHFSHPLSHYSAFSET
			LVLPETYLFTCLASFLPHYHVSFLRVRDLVRDN HCILRV*
778	85	225	<u></u>
,,,		223	MHTPHLPNIIVYFILLYICSQYLYLLTIRHNHLT
779	187	396	QSLFYNKLLSVL*
' '	10/	370	MPVTPDPSAVSLFVTPWPLLLCLPWPHRVPGQS
			HPGLHSRAPVHRLKPGPPARLQLPAAHRNLRH
780	9	210	LSIF*
/00	ן ד	218	MSWYTCQCLFFLSNTLRNGATSCHWYCSPDD
			MQMVDFSSTYERIFRPFVFKIKGPDSFRIDMSPI
701	200	100	PEDI*
781	398	192	MARSARTFLLSSTWHLTKFPMSAGYFSPCSWL
	İ		AAVIRLIQRVLMFFFFRYRALVHFTKARITVLT
500		· · · · · · · · · · · · · · · · · · ·	ANL*
782	216	791	MAGPELLLDSNIRLWVVLPIVIITFFVGMIRHYV
			SILLQSDKKLTQEQVSDSQVLIRSRVLRENGKYI
			PKQSFLTRKYYFNNPEDGFFKKTKRKVVPPSP
			MTDPTMLTDMMKGNVTNVLPMILIGGWINMT

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
.NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
İ	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
	sequence		FSGFVTTKVPFPLTLRFKPMLQQGIELLTLDAS
			WVSSASLGTSPMVFGLRSIYSSDSGPR*
783	285	440	MLFVVLPLLIIVFNIPMREAVFDFLFMIKIIKVLK
			VFYCIACFIIKQALVF*
784	277	471	MVTYFIKCFHYEVSFLLWFAVVRNDVDRPVSL
			SLFSSYSLFSTYPDTCPLFKLPTHLLCCLEEI*
785	256	429	MAVPIMLFYFSLLYKSLAFFESYSFAEYHPPTSG
			RQGCVKDILKRLIWFLIHLHLDAG
786	412	672	MAVKNVALVITWAYGFVKVTLSLLVFCVYCM
			YVILHLRMYITHKGACRHMSASWLATNCLWP
		<u>-</u>	WGCHSTFHLEIENNNTIILLELCA*
787	778	975 .	MFGVSGFCLLFTFLELVLLGLGRWWRTWKHK
			SSSSKYFLTSESTRRHKKATDSLPVVETKEQFQ
			EA
788	15	1334	MAAARCWRPLLRGPRLSLHTAANAAATATET
			TCQDVAATPVARYPPIVASMTADSKAARLRRIE
		•	RWQATVHAAESVDEKLRILTKMQFMKYMVYP
			QTFALNADRWYQYFTKTVFLSGLPPPPAEPEPE
			PEPEPEPALDLAALRAVACDCLLQEHFYLRRRR
			RVHRYEESEVISLPFLDQLVSTLVGLLSPHNPAL
			AAAALDYRCPVHFYWVRGEEIIPRGHRRGRID
			DLRYQIDDKPNNQIRISKQLAEFVPLDYSVPIEIP
			TIKCKPDKLPLFKRQYENHIFVGSKTADPCCYG
			HTQFHLLPDKLRRERLLRQNCADQIEVVFRAN
	:		AIASLFAWTGAQAMYQGFWSEADVTRPFVSQ
			AVITDGKYFSFFCYQLNTLALTTQADQNNPRK
			NICWGTQSKPLYETIEDNDVKGFNDDVLLQIVH
		•	FLLNRPKEEKSQLLEN*
789	680	880	MGLFAIHISSWLLRACFLIIENFESVLYISNTHPFI
			YMGLHRFFSQPSVWILLFLTGPLNTKSYYH*
790	85	315	MFKVVFCFGLVWFCFQRAHKPIRFEKHNFTINE
			GNLFSMNIPIVTIRSHHRTSCYHKLITCEQQTVF
	·		TNIKRHSKL*
791	112	273	MNLYLFAVLFFYVFLHIKIIFICFATKWHNLFSK
			FSYFCILHVKALSLNLGSG*
792	142	297	MYSLSLQLPVLCVLKSFKAYSLLWGVSTGVKE
700	105		GFAGRTIVNHESYYLRIVW*
793	127	315	MCTLFMHLLFCHLQSIQLKQELRLNYLTLTQF
			WQRCYSEMIFFCLSKVFLHVFQDGLEHHLE*
794	1401	1553	MFATTLGVMGLWSGIIICTVFQAVCFLGFIIQLN
			WKKACQQGALKTLKEF*
795	181	390	MHLTLSLLLFSLHFPTYIIRVNFCLVSNLFQRMR
			STKLLRLIDLDFSFTFSLLDLPPVNEYDMYIRNF

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	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
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	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	Sequence	deletion, \=possible nucleotide insertion
	Sequence		GK
796	849	1322	MVKSVIFLSFWQGMLLAILEKCGAIPKIHSARV
7,70	647	1322	SVGEGTVAAGYQDFIICGEMFFAALALRHAFT
			YKVYADKRLDAQGRCAPMKSISSSLKETMNPH
			DIVQDAIHNFSPAYQQYTQQSTLEPGPTWRGG
			AHGLSRSHSLSGARDNEKTLLLSSDDEF*
797	80	271	MGKKVTLLLQKCAWLLLVCCLFTGIKYLNKCF
131	00	271	ITDRELLRDVHNALNILRHNFYVNWASLNTF*
798	249	518	MVQLFIPILKFQLGYSVLSLCNHVLEFLFPSSLS
130	247	310	GIFSSSLPLLLPFPLSLPSLPPSLFPSLRVLLCHPH
			WSVASNSWAVAILLPQPPE*
799	481	651	MYLLILLSTKFSCISSLPGLDYRQDSMLCQGISL
133	701	051	APTLLIIHLFMCIMIKYKPLIR*
800	148	288	MCVHPYVCTCACMHVCVCLCAWCLSQPGGLG
600	140	200	GFSEEVTSLPRPRAL*
801	154	510	MLFLKKIQFLKCNKVFRSLDFCVALPLLFSSSA
1 601	1134	1310	VLQITPVDTFSDPHLVLTLVKLLMNILNIAVISL
		·	TFPGEYEVSLAFENILMYTHAFIICFCNRQWLFK
ł			SNSESNLSSNVNLFDSC*
802	99	434	MOLHGKGSQDPSTKGHIKALQTVTSFLLLCAIY
552		""	FLSMIISVCNFGRLEKQPVFMFCQAIIFSYPSTHP
			FILILGNKKLKQIFLSVLRHVRYWVKDRSLRLH
			RFTRGALCVF*
803	1189	233	MAPWAEAEHSALNPLRAVWLTLTAAFLLTLLL
			QLLPPGLLPGCAIFQDLIRYGKTKCGEPSRPAAC
			RAFDVPKRYFSHFYIISVLWNGFLLWCLTQSLF
			LGAPFPSWLHGLLRILGAAQFQGGELALSAFLV
			LVFLWLHSLRRLFECLYVSVFSNVMIHVVQYC
			FGLVYYVLVGLTVLSQVPMDGRNAYITGKNLL
			MQARWFHILGMMMFIWSSAHQYKCHVILGNL
			RKNKAGVVIHCNHRIPFGDWFEYVSSPNYLAE
			LMIYVSMAVTFGFHNLTWWLVVTNVFFNQAL
			SAFLSHQFYKSKFVSYPKHRKAFLPFLF*
804	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
			PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
	1		GTLYLQMNSLRADDTARYYCAKGGVELASTK
			PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
	1		GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
	1		SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ

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	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
ļ	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	soquence	deletion, \=possible nucleotide insertion
	sequence		SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
			HKVYACEVTHQGLSSPVTKSFNRGEC*
805	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
003	1 22	1240	PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
	}		GTLYLQMNSLRADDTARYYCAKGGVELASTK
			PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
	1		SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ
			SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
			HKVYACEVTHQGLSSPVTKSFNRGEC*
806	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
800	172	1240	PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
			GTLYLQMNSLRADDTARYYCAKGGVELASTK
			PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
			SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
}			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
<u> </u>			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
	}		LKSGTASVVCLLNNFYPREAKVQWKVDNALQ
			SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
			HKVYACEVTHQGLSSPVTKSFNRGEC*
807	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
007	92	1240	1
			PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
			GTLYLQMNSLRADDTARYYCAKGGVELASTK
	:		PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
			SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ
			SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
000	62	202	HKVYACEVTHQGLSSPVTKSFNRGEC*
808	63	203	MFPPYFSLILLLFTFASKFFLSLNLKKSNIVKARI
900	157	207	ESTKTVISKRC*
809	157	387	MQSVIRKQFTALAGFCFWFCLFTLAVLSLTLLI
			CKLRIMPFKLEGLFQELNKSWHMKLLSQDRELI
			NMLLLLMGRS*

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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ŀ	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
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<u> </u>	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
Ì	sequence	5-4	deletion, \=possible nucleotide insertion
810	50	3616	MDLPRGLVVAWALSLWPGFTDTFNMDTRKPR
0.0		3010	VIPGSRTAFFGYTVQQHDISGNKWLVVGAPLET
			NGYQKTGDVYKCPVIHGNCTKLNLGRVTLSNV
			SERKDNMRLGLSLATNPKDNSFLACSPLWSHE
			CGSSYYTTGMCSRVNSNFRFSKTVAPALQRCQ
			TYMDIVIVLDGSNSIYPWVEVQHFLINILKKFYI
			GPGQIQVGVVQYGEDVVHEFHLNDYRSVKDV
			VEAASHIEQRGGTETRTAFGIEFARSEAFQKGG
			RKGAKKVMIVITDGESHDSPDLEKVIQQSERDN
			VTRYAVAVLGYYNRRGINPETFLNEIKYIASDP
		Ì	DDKHFFNVTDEAALKDIVDALGDRIFSLEGTNK
			NETSFGLEMSQTGFSSHVVEDGVLLGAVGAYD
1			WNGAVLKETSAGKVIPLRESYLKEFPEELKNH
			GAYLGYTVTSVVSSRQGRVYVAGAPRFNHTG
			KVILFTMHNNRSLTIHQAMRGQQIGSYFGSEITS
			VDIDGDGVTDVLLVGAPMYFNEGRERGKVYV
		1	YELRONRFVYNGTLKDSHSYQNARFGSSIASV
			RDLNQDSYNDVVVGAPLEDNHAGAIYIFHGFR
			GSILKTPKQRITASELATGLQYFGCSIHGQLDLN
			EDGLIDLAVGALGNAVILWSRPVVQINASLHFE
			PSKINIFHRDCKRSGRDATCLAAFLCFTPIFLAP
1			HFQTTTVGIRYNATMDERRYTPRAHLDEGGDR
		ŀ	FTNRAVLLSSGQELCERINFHVLDTADYVKPVT
			FSVEYSLEDPDHGPMLDDGWPTTLRVSVPFWN
			GCNEDEHCVPDLVLDARSDLPTAMEYCQRVLR
			KPAQDCSAYTLSFDTTVFIIESTRQRVAVEATLE
			NRGENAYSTVLNISQSANLQFASLIQKEDSDGSI
1			ECVNEERRLQKQVCNVSYPFFRAKAKVAFRLD
			FEFSKSIFLHHLEIELAAGSDSNERDSTKEDNVA
			PLRFHLKYEVDVLFTRSSSLSHYEVKPNSSLER
			YDGIGPPFSCIFRIQNLGLFPIHGMMMKITIPIAT
			RSGNRLLKLRDFLTDEANTSCNIWGNSTEYRPT
			PVEEDLRRAPQLNHSNSDVVSINCNIRLVPNQEI
	·		NFHLLGNLWLRSLKALKYKSMKIMVNAALQR
			QFHSPFIFREEDPSRQIVFEISKQEDWQVPIWIIV
			GSTLGGLLLLALLVLALWKLGFFRSARRREP
811	261	410	GLDPTPKVLE*
011	201	419	MALNIINPVWFCHCLTCTIHIDFHILFIKIFKHM
013	140	1202	FFRSLWSSWLSHQLDHI*
812	49	282	MAIFPLWKGVNVLVCIFSSFIMLNIYCTLLIWKF
			IYSAFFCYITSLMIFPFSFFCSFFLDLLKVIVYIFF
012	1147	202	LYLYSSR*
813	147	293	MGYLLWLVLSILVCTELGLGRLTFPLDSESPRT

SEQ ID Predicted beginning nucleotide location corresponding to first amino  NO: Predicted end heginning nucleotide location corresponding to first amino  Amino acid segment containing (A=Alanine C=Cysteine, D=A E=Glutamic Acid, F=Phenylal H=Histidine, I=Isoleucine, K= M=Methionine, N=Asparaging	Aspartic Acid,
nucleotide location E=Glutamic Acid, F=Phenylal location corresponding to first amino M=Methionine, N=Asparaging	
location corresponding H=Histidine, I=Isoleucine, K= corresponding to first amino M=Methionine, N=Asparagine	lanine, G=Glycine,
corresponding to first amino M=Methionine, N=Asparagine	
to first amino acid residue of Q=Glutamine, R=Arginine, S=	•
acid residue   amino acid   V=Valine, W=Tryptophan, Y=	
of amino acid   sequence   X=Unknown, *=Stop codon, /	
sequence deletion, \=possible nucleotide	e insertion
SYKVRPWVVLEAWVW*	
814 418 155 MCLSHLVSLFPAATAFLIN	KVPLPVDKLAPLPL
DNILPFMDPLKLLLKTLGIS	SVEHLVEGLRKCVN
ELGPEASEAVKKLLEALSH	ILV*
815 32 742 MAWIPLFLGVLAYCTGAV	
GQTASITCSGDRLGDKIAC	
HQDTKRPSGIPERFSGSNSG	
DEADYYCQAWDSSSYVAF	
AAPSVTLFPPSSEELQANKA	
TVAWKADSSPVKAGVETT	
YLSLTPEQWKSHRSYSCQV	-
TEYLLRVY*	VIIIEGSIVERIVAF
	LL CCCCCODDD DDD
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
PAAAAAAGGQLLGDGGS	` `
GFLYRRLKTQEKREMQKE	
GLQQPQPPALRQQEEQQQQ	
KSAPLFMLDLYNALSADNI	
WPHEAASSSQRRQPPPGAA	
GSGGASPLTSAQDSAFLND	
DKEFSPRQRHHKEFKFNLS	
YKDCVMGSFKNQTFLISIY	
LLDTRVVWASKEGWLEFD	DITATSNLWVVTPQH
NMGLQLSVVTRDGVHVHF	PRAAGLVGRDGPYD
KQPFMVAFFKVSEVHVRT	TRSASSRRRQQSRN
RSTQSQDVARVSSASDYNS	SSELKTACRKHELY
VSFQDLGWQDWIIAPKGYA	AANYCDGECSFPLN
AHMNATNHAIVQTLVHLM	INPEYVPKPCCAPT
KLNAISVLYFDDNSNVILKI	KYRNMVVRACGCH
*	
817 7 942 MGCRLLCCAVLCLLGAVP	METGVTOTPRHLV
MGMTNKKSLKCEQHLGHN	
LELMFVYNFKEQTENNSVE	
LHLHTLQPEDSALYLCASS	
TRLTVLEDLKNVFPPEVAV	
TLVCLATGFYPDHVELSWY	~ 1
DPQPLKEQPALNDSRYCLS	
RNHFRCQVQFYGLSENDEV	WICHDARDUTOIVE
AEAWGRADCGFTSESYQQ	
818 1355 1672 MALLCICLCLIFFLIVKARR	
in the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contract of the contrac	KQAAGKPEKMDDE
DPIMGTITSGSRKKPWPDSF	PODQASPPGDAPPL
EEQKELHYASLSFSEMKSR	EPKDQEAPSTTEYS
EIKTSK*	

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	1		
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
819	3461	3685	MVVGIVAAAALCILILLYAMYKYRNRDEGSYQ
			VDETRNYISNSAQSNGTLMKEKQQSSKSGHKK
			QKNKDREYYV*
820	3461	3685	MVVGIVAAAALCILILLYAMYKYRNRDEGSYQ
		1	VDETRNYISNSAQSNGTLMKEKQQSSKSGHKK
			QKNKDREYYV*
821	129	272	MGSLMPLRPLALHTALGAALNFSLPCEWSTLPS
			ASEAGRLWGPPSFQ*
822	98	1474	MAWASRLGLLLALLLPVVGASTPGTVVRLNK
			AALSYVSEIGKAPLQRALQVTVPHFLDWSGEA
	,		LQPTRIRILNVHVPRLHLKFIAGFGVRLLAAANF
			TFKVFRAPEPLELTLPVELLADTRVTQSSIRTPV
			VSISACSLFSGHANEFDGSNSTSHALLVLVQKHI
			KAVLSNKLCLSISNLVQGVNVHLGTLIGLNPVG
			PESQIRYSMVSVPTVTSDYISLEVNAVLFLLGKP
			IILPTDATPFVLPRHVGTEGSMATVGLSQQLFDS
			ALLLLQKAGALNLDITGQLRSDDNLLNTSALG
			RLIPEVARQFPEPMPVVLKVRLGATPVAMLHT
			NNATURLQPFVEVLATASNSAFQSLFSLDVVVN
			LRLQLSVSKVKLQGTTSVLGDVQLTVASSNVG
			FIDTDQVRTLMGTVFEKPLLDHLNALLAMGIA
			LPGVVNLHYVAPEIFVYEGYVVISSGLFYQS*
823	177	377	MKLVLLRKTSLSVFTTLFSVSSSQYPVLSTSICN
023	*′′	377	TPVFSTLFLEACSVNPLPSTVFLVLLYSVACL*
824	1629	1123	MIFVLGQAEGILIMLAMTALTVRRSEPSLSTCQ
024	102)	1125	QGEDPLDWTVSLLLMAGLCTFFSCILAVFFHTP
			YRRLQAESGEPPSTRNAVGSQTQGRVWTEGEA
Ī			RKGLGSWGPARRIPELHGEGGASLRGPQEGHG
			SPHPACHRATPRAQGPAATDAPFPPGQTRRQGP
825	381	572	SVQVY*
623	301	372	MLLAKRYAKYFIYFIFFNPVLIPILQRRILRLGEI
926	750	610	HIAGQCRAGSLQSLPLPANLHSILDILA*
826	758	618	MLLCLHLIIICLVFCIISAIPWVLNQCLIFRLYFLC
027	104	260	QKKLAMSLEN*
827	184	360	MLIGSGYLCFCALQWTELGNVCVCAHICRCTH
000	140	1	MQVSGITSPVHVHIHRVLSCLIHFTS*
828	140	355	MHLLVSHAFLPFPLHGYSGRQRGAKQWRCHP
			ARASRERPSEDNLSPAVKEESGFVVSEHLAALH
			RKLRGCH*
829	21	956	MLLLLLLGLAGSGLGAVVSQHPSWVICKSGT
			SVKIECRSLDFQATTMFWYRQFPKQSLMLMAT
			SNEGSKATYEQGVEKDKFLINHASLTLSTLTVT
			SAHPEDSSFYICSAGADSGTQETQYFGPGTRLT
	<del></del>	<del></del>	

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,	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
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	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
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	sequence	sequence	deletion, \=possible nucleotide insertion
	3cquerice		VLEDLKNVFPPEVAVFEPSEAEISHTQKATLVC
			LATGFYPDHVELSWWVNGKEVHSGVSTDPQP
			LKEQPALNDSRYCLSSRLRVSATFWQNPRNHF
ļ			RCQVQFYGLSENDEWTQDRAKPVTQIVSAEA
			WGRADCGFTSESYQQGVLSATILYEILLGKATL
			YAVLVSALVLMAMVKRKDSRG*
830	134	292	MSVGLHLGFLAWFLPFLIPTSPLPLLFQLGALPN
050	134	292	ESLALYAWLRDCFWENIT*
831	58	258	MSSPCFQCFHLCCTIKVWPLCHHLQKAFPDFSI
651	30	236	HVFSESDLSSFCEVQLLKICLQKYFLGSLMHCS*
832	68	259	MIKLCHOLYNVYVCFFHLIVLGDIAIDYIIVPNIS
632	08	239	
833	290	430	YLSISIPFVVTNIRGRDIFHPCNVALVM*
833	290	430	MFYENKRREYLQDMLLSYRLLVAILVLLKKLT
834	112	267	ELNTITLICKSIIF*
834	112	267	MNIVFVILLFKDMQVLEVFVLLNVLTTLTIIAA
835	50	240	GILCTSFCCKPFIYINPL*
833	58	240	MIRFALPWFSQIWLSKQTWTRLTHLAFLLQEC
836	30	206	NSMFYPKVSRTTVFGCLFNPLSSRVCFE*
630	30	296	MTNFFHLLLPLLPSLFSPSSKTHSFNIHKIIIILFF
			NSIFLYPRDYLKIRNWLQSNTLEREIEWITSIRCL
837	1089	062	CNSGTTFIFPLTTKST*
837	1089	952	MLYLLEFPGVSYLRSLFLGRPIGPGITSDFTLILF
838	500	(70	SNLLDSWPLS*
828	300	670	MPCSVPETLFSLLWLAPSHHSGFSSNEASLRTD
839	0.4	061	LLFATAILYSLWHPPYYFLYNTS*
839	84	251	MLFTSFVYGLIFILFDFYFLSFVERDVKIFNCNG
040	00	245	EIVLFPFNSVHFCLICLYIHI*
840	99	245	MILNLSSLTLVFAWNYPLHLMISLNVSCSCYSD
041	00	005	DISGIYRSVLRQKLG*
841	82	297	MCLILVIWKIHYAELIMLNKRVVNKCRSCLIQK
İ			CLSTCHSTVIVLYQCREEEAVMLIKLNFKMKIQ
			RTICI*
842	36	275	MNLKRLLLFLAKMFSAIFSLPTHPSHFPISIYDNI
İ			GHWPQSPKVRRKEGNEYLLNPNMCQTLDLTLL
			GIGDYLTSITSP*
843	165	437	MAPLPSLTLRPWCVLMLLDLWAAFGTITPSLK
			HFHHLPSGTQHSLVFVLSLTLHSQLSLLMGTSA
			VCLSACFSSLSTFPGWLLIICTLMI*
844	322	462	MFLLDLCLGSLSVFIDTHPCMHGGFKCSQDWC
			SPAKLLLSAFTKTR*
845	182	358	MLSLVKLLLLCIIHDHSINFCIAIQVGLLPSAYR
ļ			VPGIVLSLENTALIRQTPCSNRAN*
846	98		

SEQ ID NO:	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion PDAPLSSAAYSIRSIGERPVLKAPVPKRQKCDH WTPCPSDTYAYRLLSGGGRSKYAKICFEDNLL MGEQLGNVARGINIAIVNYVTGNVTATRCFDM YEGDNSGPMTKFIQSAAPKSLLFMVTYDDGST RLNNDAKNAIEALGSKEIRNMKFRSSWVFIAA KGLELPSEIQREKINHSDAKNNRYSGWPAEIQIE
847	1608	1805	GCIPKERS*  MLPFCHLWVPVTLVAAGAAQPAASMVMFPHL PALHHHCPHSHRTSQYMPASDGPQAYPDYAD
848	386	592	QST* MNPCFCGFLVLLSCCLSLLDSQLHNLIALQITCF KDVEIPNFFCDPSQLPHHACCDTFTNNIVMYFP AA
849	1074	2294	MLLLLLLPLLWGTKGMEGDRQYGDGYLLQV QELVTVQEGLCVHVPCSFSYPQDGWTDSDPVH GYWFRAGDRPYQDAPVATNNPDREVQAETQG RFQLLGDIWSNDCSLSIRDARKRDKGSYFFRLE RGSMKWSYKSQLNYKTKQLSVFVTDPPWNLT MTVFQGDATASTALGNGSSLSVLEGQSLRLVC AVNSNPPARLSWTRGSLTLCPSRSSNPGLLELP RVHVRDEGEFTCRAQNAQGSQHISLSLSLQNE GTGTSRPVSQVTLAAVGGAGATALAFLSFCIIFI IVRSCRKKSARPAAGVGDTGMEDAKAIRGSAS QGPLTESWKDGNPLKKPPPAVAPSSGEEGELH YATLSFHKVKPQDPQGQEATDSEYSEIKIHKRE TAETQACLRNHNPSSKEVRG*
850	100	318	MYYTLCNFVFFTLHMILFPKSLNILLSNQIRSAI VHLKQRTSCIKNQPEPYQRADAMNTNHSLVAV PYVNLI*
851	328	549	MFWMVKILTPKASTFQVTTSVSVPLTSATGAA CSGSCFHSTGCAGRPQTHAGAPCASEQNSRNE VMQTSTNEM*
852	162	440	MHCRQLKEVLQLPLTCSSCCVCTMTVAFPSVQ QVWMETVLTLGGLDAAQDEIQAVRLILLPESSP QGPHGNLAPCSAKPFFLPQVMPLGTAP*
853	39	839	MVCLRLPGGSCMAVLTVTLMVLSSPLALAGDT RPRFLEYSTSECHFFNGTERVRFLDRYFYNQEE YVRFDSDVGEFRAVTELGRPDEEYWNSQKDFL EDRRAAVDTYCRHNYGVVESFTVQRRVHPKV TVYPSKTQPLQHHNLLVCSVSGFYPGSIEVRWF RNGQEEKTGVVSTGLIHNGDWTFQTLVMLETV PRSGEVYTCQVEHPSVTSPLTVEWRARSESAQS KMLSGVGGFVLGLLFLGAGLFIYFRNQKGHSG

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	1	1 11	X=Unknown, *=Stop codon, /=possible nucleotide
	of amino acid	sequence	deletion, \=possible nucleotide insertion
	sequence		LOPRGFLS*
054		1024	1
854	54	1034	MMSPSQASLLFLNVCIFICGEVVQGNCVHHSTD
	Į		SSVVNIVEDGSNAKDESKSNDTVCKEDCEESC
1			DVKTKITREEKHFMCRNLQNSIVSYTRSTKKLL
			RNMMDEQQASLDYLSNQVNELMNRVLLLTTE
	ļ		VFRKQLDPFPHRPVQSHGLDCTDIKDTIGSVTK
			TPSGLYIIHPEGSSYPFEVMCDMDYRGGGWTVI
			QKRIDGIIDFQRLWCDYLDGFGDLLGDAFRGL
			KKEDNQNAMPFSTSDVDNDGCRPACLVNGQS
			VKSCSHLHNKTGWWFNECGLANLNGIHHFSG
			KLLATGIQWGTWTKNNSPVKIKSVSMKIRRMY
			NPYFK*
855	124	336	MRTWSKVIPSLWLKFSRGFIILRFHFLMIIWPDIP
			SSMYICMSFITAFKNLFMFGINRIKKISVVSRNT
			L*
856	159	1028	MGLCVPFAVTTSFLSLGLEWDLNVRLHGQHLV
			QQLVLRTVRGYLETPQPEKALALSFHGWSGTG
!			KNFVARMLVENLYRDGLMSDCVRMFIATFHFP
	•		HPKYVDLYKEQLMSQIRETQQLCHQTLFIFDEA
		]	EKLHPGLLEVLGPHLERRAPEGHRAESPWTIFL
			FLSNLRGDIINEVVLKLLKAGWSREEITMEHLE
			PHLQAEIVETIDNGFGHSRLVKENLIDYFIPFLPL
			EYRHVRLCARDAFLSQELLYKEETLDEIAQMM
			VYVPKEEQLFSSQGCKSISQRINYFLS*
857	182	334	MKSSNIFSLFLFLVTFIFLTSIASILFSSWCPFSLIK
			CNQDLYYSGNGAS*
858	35	172	MLCSLFHILIVTLLLAISFGMSSRNTLNMVNSKI
	,		KEHSLHRKLEI*
859	6	215	MFWTLVQGMSLLCLTDVFQALPSICIANSEIYY
037	"	213	TVLTLMQFNCLWMVLSGKKVIFSSELMVRKGR
•			RSWK*
860	204	350	MYLKPLIYFSILIFLSQRSKLSLPYNVHNCMNIG
800	204	330	EDRRPQKVQLLQLY*
861	263	412	MLPLALIVDLIYPWVQVRGPEDPNHGTTERKR
001	203	712	
962	160	970	EEVTCLGAARLSLEAAR*
862	169	879	MTAEFLSLLCLGLCLGYEDEKKNEKPPKPSLHA
			WPSSVVEAESNVTLKCQAHSQNVTFVLRKVND
1			SGYKQEQSSAENEAEFPFTDLKPKDAGRYFCA
			YKTTASHEWSESSEHLQLVVTDKHDELEAPSM
			KTDTRTIFVAIFSCISILLLFLSVFIIYRCSQHSSSS
			EESTKRTSHSKLPEQEAAEADLSNMERVSLSTA
			DPQGVTYAELSTSALSEAASDTTQEPPGSHEYA
			ALKV*
	.i.	L	1

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
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	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
1	sequence	sequence	deletion, \=possible nucleotide insertion
863	114	1031	MPLLTLYLLFWLSGYSIATQITGPTTVNGLER
003	114	1031	GSLTVQCVYRSGWETYLKWWCRGAIWRDCKI
			LVKTSGSEQEVKRDRVSIKDNQKNRTFTVTME
			DLMKTDADTYWCGIEKTGNDLGVTVQVTIDP
			ASTPAPTTPTSTTFTAPVTQEETSSSPTLTGHHL
			DNRHKLLKLSVLLPLIFTILLLLLVAASLLAWR
			MMKYQQKAAGMSPEQVLQPLEGDLCYADLTL
			QLAGTSPQKATTKLSSAQVDQVEVEYVTMASL
			PKEDISYASLTLGAEDQEPTYCNMGHLSSHLPG
			RGPEEPTEYSTISRP*
864	64	435	MRISCPWCLWNLSLEVGGTVATTAQQHIAEVC
			RSSQAGRGFLHCLHPALGTSGCHPVPCSSSLVG
			FGWRGYSGEASWGRASSRPAAPTPPMPANVQ
			AGWEQSVRLLCHSWLRLAALHVTHEES*
865	391	528	MSQQSWFTVYLFYLLRSNIWLEMGIPKYVKEV
			ELRSLDFTSNYFS*
866	46	612	MDWTWRFLFVVAAATGVQSQVQLVQSGAEV
			KKPGSSVKVSCKASGGTFSTYAISWVRQAPGQ
			GLEWMGGIIPIFGTANYAQKFQGRVTITADEST
			STAYMELSSLRSEDTAVYYCARVWGGSGSYYS
			IVSTIGATTTVWMSGAREPWSPSPQPPPRAHRS
			SPWHPPPRAPLGAQRPWAAWSRTTSPNR*
867	46	612	MDWTWRFLFVVAAATGVQSQVQLVQSGAEV
1			KKPGSSVKVSCKASGGTFSTYAISWVRQAPGQ
			GLEWMGGIIPIFGTANYAQKFQGRVTITADEST
			STAYMELSSLRSEDTAVYYCARVWGGSGSYYS
			IVSTIGATTTVWMSGAREPWSPSPQPPPRAHRS
			SPWHPPPRAPLGAQRPWAAWSRTTSPNR*
868	133	960	MACPGFLWALVISTCLEFSMAQTVTQSQPEMS
			VQEAETVTLSCTYDTSESDYYLFWYKQPPSRQ
İ			MILVIRQEAYKQQNATENRFSVNFQKAAKSFSL
1			KISDSQLGDAAMYFCAYRSGRDDKIIFGKGTRL
	}		HILPNIQNPDPAVYQLRDSKSSDKSVCLFTDFDS
			QTNVSQSKDSDVYITDKTVLDMRSMDFKSNSA
			VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCD
1			VKLVEKSFETDTNLNFQNLSVIGFRILLLKVAG
			FNLLMTLRLWSS*
869	164	310	MVLRLPWWGVLAYGNDVGFGFYSFLCYQINP
			PTCPILWLWEVLTVGKS*
870	959	1252	MEFLGPCGLRLVGARPLLPYWLLVFLAALNAL
""		1 - 2 - 2	LQWLLRPLVLYAPLLNPYTLAVANTTFTVSTD
	}		KAQRHFGYEPPFSWEDSRTRTILWVQAATGSA
			Q*
L			<u>                                     </u>

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	
	to first amino	acid residue of	M=Methionine, N=Asparagine, P=Proline,
		i	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
871	52	828	MPRPRRVSQLLDLCLWCFMKNISRYLTDIKPLP
			PNIKDRLIKIMSMQGQITDSNISEILHPEVQTLDL
			RSCDISDAALLHLSNCRKLKKLNLNASKGNRV
		•	SVTSEGIKAVASSCSYLHEASLKRCCNLTDEGV
			VALALNCQLLKIIDLGGCLSITDVSLHALGKNC
	†		PFLQCVDFSATQVSDSGVIALVSGPCAKKLEEI
			HMGHCVNLTDGAVEAVLTYCPQIRILLFHGCP
			LITDHSREVLEQLVGPNKLKQVTWTVY*
872	313	1704	MLLLLLPLLWGRERAEGQTSKLLTMQSSVTVQ
<u> </u>			EGLCVHVPCSFSYPSHGWIYPGPVVHGYWFRE
			GANTDQDAPVATNNPARAVWEETRDRFHLLG
Ì			DPHTENCTLSIRDARRSDAGRYFFRMEKGSIKW
			NYKHHRLSVNVTALTHRPNILIPGTLESGCPQN
}			LTCSVPWACEQGTPPMISWIGTSVSPLDPSTTRS
			SVLTLIPQPQDHGTSLTCQVTFPGASVTTNKTV
	1		HLNVSYPPQNLTMTVFQGDGTVSTVLGNGSSL
			SLPEGQSLRLVCAVDAVDSNPPARLSLSWRGL
			TLCPSQPSNPGVLELPWVHLRDEDEFTCRAQNP
			LGSQQVYLNVSLQSKATSGVTQGAVGGAGAT
		İ	ALVFLSFCVIFVVVRSCRKKSARPAAGVGDTGI
			EDANAVRGSASQGPLTEPWAEDSPPDQPPPAS
			ARSSVGEGELQYASLSFQMVKPWDSRGQEATD
			TEYSEIKIHR*
873	590	766	MLFGLALQLILDLKLTTVNQRESDVARVATAE
			EYSKKGLLGQETLHAGSQTRMQILIS*
874	206	418	MLKLLCAAEVTNVLFNCVFDYGCPKTFCHPWT
			IFVLFWSSLEGGFIISYKTLTGALECRFLITLEIVT
			SE*
875	241	957	MRSSLTMVGTLWAFLSLVTAVTSSTSYFLPYW
			LFGSQMGKPVSFSTFRRCNYPVRGEGHSLIMVE
			ECGRYASFNAIPSLAWQMCTVVTGAGCALLLL
			VALAAVLGCCMEELISRMMGRCMGAAQFVGG
			LLISSGCALYPLGWNSPEIMQTCGNVSNQFQLG
			TCRLGWAYYCAGGGAAAAMLICTWLSCFAGR
			NPKPVILGGKHHEENHFLCYGAWPLPSTLELRK
			EDRGGRATGKQVTP
876	241	957	MRSSLTMVGTLWAFLSLVTAVTSSTSYFLPYW
3.0	- · ·	,,,	LFGSQMGKPVSFSTFRRCNYPVRGEGHSLIMVE
			, ,
į			ECGRYASFNAIPSLAWQMCTVVTGAGCALLLL
			VALAAVLGCCMEELISRMMGRCMGAAQFVGG
		·	LLISSGCALYPLGWNSPEIMQTCGNVSNQFQLG
			TCRLGWAYYCAGGGAAAAMLICTWLSCFAGR
	<u> </u>		NPKPVILGGKHHEENHFLCYGAWPLPSTLELRK

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
1.10.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
ļ	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
ļ	sequence		EDRGGRATGKQVTP
877	136	1710	MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLA
0//	130	1710	RILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
			LGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIP
1			FIVLCHPDTIRSITNASAAIAPKDNLFIRFLKPWL
			GEGILLSGGDKWSRHRRMLTPAFHFNILKSYITI
			FNKSANIMLDKWQHLASEGSSCLDMFEHISLM
			TLDSLQKCIFSFDSHCQERPSEYIATILELSALVE
		İ	KRSQHILQHMDFLYYLSHDGRRFHRACRLVHD
			FTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFI
			DVLLLSKDEDGKALSDEDIRAEADTFMFGGHD
			TTASGLSWVLYNLARHPEYQERCRQEVQELLK
			DRDPKEIEWDDLAQLPFLTMCVKESLRLHPPAP
			FISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNP
			TVWPDPEVYDPFRFDPENSKGRSPLAFIPFSAGP
			RNCIGQAFAMAEMKVVLALMLLHFRFLPDHTE
070	126	1710	PRRKLELIMRAEGGLWLRVEPLNVSLQ*
878	136	1710	MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLA
	,		RILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
			LGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIP
			FIVLCHPDTIRSITNASAAIAPKDNLFIRFLKPWL
			GEGILLSGGDKWSRHRRMLTPAFHFNILKSYITI
1			FNKSANIMLDKWQHLASEGSSCLDMFEHISLM
		·	TLDSLQKCIFSFDSHCQERPSEYIATILELSALVE
		-	KRSQHILQHMDFLYYLSHDGRRFHRACRLVHD
			FTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFI
			DVLLLSKDEDGKALSDEDIRAEADTFMFGGHD
			TTASGLSWVLYNLARHPEYQERCRQEVQELLK
			DRDPKEIEWDDLAQLPFLTMCVKESLRLHPPAP
			FISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNP
			TVWPDPEVYDPFRFDPENSKGRSPLAFIPFSAGP
			RNCIGQAFAMAEMKVVLALMLLHFRFLPDHTE
970	126	1710	PRRKLELIMRAEGGLWLRVEPLNVSLQ*
879	136	1710	MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLA
		1	RILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
			LGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIP
			FIVLCHPDTIRSITNASAAIAPKDNLFIRFLKPWL
			GEGILLSGGDKWSRHRRMLTPAFHFNILKSYITI
			FNKSANIMLDKWQHLASEGSSCLDMFEHISLM
			TLDSLQKCIFSFDSHCQERPSEYIATILELSALVE
			KRSQHILQHMDFLYYLSHDGRRFHRACRLVHD
			FTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFI
	<u> </u>	<u></u>	DVLLLSKDEDGKALSDEDIRAEADTFMFGGHD

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
	•		TTASGLSWVLYNLARHPEYQERCRQEVQELLK
			DRDPKEIEWDDLAQLPFLTMCVKESLRLHPPAP
			FISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNP
			TVWPDPEVYDPFRFDPENSKGRSPLAFIPFSAGP
			RNCIGQAFAMAEMKVVLALMLLHFRFLPDHTE
			PRRKLELIMRAEGGLWLRVEPLNVSLQ*
880	856	257	MRLSLPLLLLLGAWAIPGGLGVMAPLTATAP
000	830	251	EVDDEEMYSAHMPAHLRCDACRAVAYQECGP
			KTLAKAETKLHTSNSGGRRDVSELVYTDVLDR
			SCSRNWQDYGVREVDQVKRLTGPGLSEGPEPS
			ISVMVTGGPWHTRLSRTCLHYLGEFGEDQIYE
			AHQQGRGALEALLCGGPPGGLLREGVSHKRRA
			LVLDSTLL*
001	700	1222	MTLRPSLLPLHLLLLLLSAAVCRAEAGLETES
881	782	1222	PVRTLQVETLVEPPEPCAEPAAFGDTLHIHYTG
			SLVDGRIIDTSLTRDPLVIELGQKQVIPGLEQSLL
			DMCVGEKRRAIIPSHLAYGKRGFPPSVPGTKDN
	-	0040	LMRPPGMTSSSQ*
882	940	2040	MALRFLLGFLLAGVDLGVYLMRLELCDPTQRL
			RVALAGELVGVGGHFLFLGLALVSKDWRFLQ
			RMITAPCILFLFYGWPGLFLESARWLIVKRQIEE
			AQSVLRILAERNRPHGQMLGEEAQEALQDLEN
		İ	TCPLPATSSFSFASLLNYRNIWKNLLILGFTNFIA
			HAIRHCYQPVGGGGSPSDFYLCSLLASGTAALA
			CVFLGVTVDRFGRRGILLLSMTLTGIASLVLLG
			LWDYLNEAAITTFSVLGLFSSQAAAILSTLLAA
			EVIPTTVRGRGLGLIMALGALGGLSGPAQRLH
			MGHGAFLQHVVLAACALLCILSIMLLPETKRK
			LLPEVLRDGELCRRPSLLRQPPPTRCDHVPLLA
			TPNPAL*
883	133	306	MVKRKSWTKWCGWLTVVRFLARGFEMHLKS
			CSRLLFSELAAFAFFEFSLKTVTLRAF*
884	196	357	MCLMKQIIYLLYVGLCSILTAFLFTPHHVLERY
	1	, ·	RYYCPDFREIKKLGQGYTTN*
885	252	560	MKEALLKCSRLARGLLLCLDCANDHRSPVERN
			AQTTLILHSSLYSLSLGNQLQGGGEMATTGGST
			QQAKTYGGLFQIGAMEPALFLLFIFLLASFWVH
			RAIE*
886	46	189	MLETFLFKLFLFFTLLVNLFITNDQLSVGSIFLSF
			QLPAFFLDMAEF*
887	68	208	MTFLLHVLVTALSSHSTGRRGTNCFMLLSSGN
30,		-00	HPIPCGSLTPYPHL*
888	214	399	MVYLPVSLNGLRLACFSYVLAPIKVKPGGGSET
000	1 417	1 377	1414 TEL VOLINGEIGENCE DE VENERNA NEI OCOSET

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
		to first amino	M=Methionine, N=Asparagine, P=Proline,
ļ	corresponding	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	to first amino		V=Valine, W=Tryptophan, Y=Tyrosine,
	acid residue	amino acid	X=Unknown, *=Stop codon, /=possible nucleotide
]	of amino acid	sequence	X=Unknown, *=Stop codon, /-possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			RDGFRIPESTPSLKAGYCDHKHFLPTIHL
889	50	214	MTLLNLYYLNSFLLYSKRFEGISFCVQKVSIILCI
			HYLRSTTIWNKLFFRDVSA*
890	158	700	MHFPVNCFFKSLHIFLLLQVFLATFLRKKLSKV
			AFSCLVEFFYYCYYFLDFASSVSFLFCFVLLLRQ
	1		SLTLSPRLECSDTILAHCNLRLPGSRYSSASTSR
1			VAGITGVHHHTYVNFVWTVQKAVHCVGQAS
			WELLTSRDPPTLASHRAGITGMSHRTWAKVFL
			KRVIFLNREYDLTMFCFL
891	133	333	MLVPTFLSLVCDFSLFVLLLLGCLSFLLPPHLPC
ļ			TSFPLHLWRLLSPFISFLDLLLLLSYKMNCII*
892	71	295	MLPLFKHSPVRIFLFCLNTQHLSVRNNFVFNCV
			SPGILPISLCLAFNHDRSTFFFSIILLLKALIILSSL
			LQTK*
893	95	331	MKPILLVLSSITRALLLQISSVSWQSCMWRAMP
0,5			DCLQTDYPISLGFHQRTRLLDALCPVTQCHHSA
			WPCVCQGAQTPI*
894	182	418	MCCELLAVVIATLIIKIGLVVLLYFIKLLIHIEFIK
,			RHSILKCESIFNLNVGIRMYPGQVNFCETLQML
	Ì		DGFGRIFQTK
895	104	2683	MACRWSTKESPRWRSALLLLFLAGVYGNGAL
0,3	10,	2003	AEHSENVHISGVSTACGETPEQIRAPSGIITSPG
	İ		WPSEYPAKINCSWFIRANPGEIITISFQDFDIQGS
		•	RRCNLDWLTIETYKNIESYRACGSTIPPPYISSQ
1			DHIWIRFHSDDNISRKGFRLAYFSGKSEEPNCA
	·		CDOFRCGNGKCIPEAWKCNNMDECGDRSDEEI
-			CAKEANPPTAAAFQPCAYNQFQCLSRFTKVYT
			CLPESLKCDGNIDCLDLGDEIDCDVPTCGQWL
			KYFYGTFNSPNYPDFYPPGSNCTWLIDTGDHR
			KVILRFTDFKLDGTGYGDYVKIYDGLEENPHK
			LLRVLTAFDSHAPLTVVSSSGQIRVHFCADKVN
			AARGFNATYQVDGFCLPWEIPCGGNWGCYTE
		İ	OQRCDGYWHCPNGRDETNCTMCQKEEFPCSR
			NGVCYPRSDRCNYQNHCPNGSDEKNCFFCQPG
			NGVC TPRSDRCM TQMTC NGSDERIVETT EQTO NFHCKNNRCVFESWVCDSQDDCGDGSDEENC
			PVIVPTRVITAAVIGSLICGLLLVIALGCTCKLYS
			LRMFERRSFETQLSRVEAELLRREAPPSYGQLI
			AQGLIPPVEDFPVCSPNQASVLENLRLAVRSQL
		<b>†</b>	GFTSVRLPMAGRSSNIWNRIFNFARSRHSGSLA
			LVSADGDEVVPSQSTSREPERNHTHRSLFSVES
		1	DDTDTENERRDMAGASGGVAAPLPQKVPPTTA
			VEATVGACASSSTQSTRGGHADNGRDVTSVEP
L			PSVSPARHQLTSALSRMTQGLRWVRFTLGRSSS

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
		to first amino	M=Methionine, N=Asparagine, P=Proline,
	corresponding to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
		•	
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	·	deletion, \=possible nucleotide insertion
			LSQNQSPLRQLDNGVSGREDDDDVEMLIPISDG
,			SSDFDVNDCSRPLLDLASDQGQGLRQPYNATN
			PGVRPSNRDGPCERCGIVHTAQIPDTCLEVTLK
			NETSDDEALLLC*
896	230	391	MSNRTRIRTHVNLCCFCRYTTPKMSFSSACVSL
			CLMLLFCSPPLLLLLSSFV*
897	47	1147	MASMAAVLTWALALLSAFSATQARKGFWDYF
1			SQTSGDKGRVEQIHQQKMAREPATLKDSLEQD
			LNNMNKFLEKLRPLSGSEAPRLPQDPVGMRRQ
			LQEELEEVKARLQPYMAEAHELVGWNLEGLR
			QQLKPYTMDLMEQVALRVQELQEQLRVVGED
		ļ	TKAQLLGGVDEAWALLQGLQSRVVHHTGRFK
			ELFHPYAESLVSGIGRHVQELHRSVAPHAPASP
	1	1	ARLSRCVQVLSRKLTLKAKALHARIQQNLDQL
			REELSRAFAGTGTEEGAGPDPQMLSEEVRQRL
			QAFRQDTYLQIAAFTRAIDQETEEVQQQLAPPP
			PGHSAFAPEFQQTDSGKVLSKLQARLDDLWED
			ITHSLHDQGHSHLGDP*
898	493	636	MFIGLGISFLNCPSLFAHFILFCPLPLFGIFISYWF
			VRLLSINRGWK*
899	92	1195	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
			PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
		•	EWVSGFTGSGGSGGSTYYADSVKGRFTISRDN
			SKNTLFLQMNSLRAEDTAVYYCAKGLLPPRW
			AYRVYEDSGIFFDYWGQGTLVTVSSSDIQMTQ
			SPSTLSASVGDRVTITCRASQSISSWLAWYQQK
			PGKAPKLLIYKASSLQSGVPSRFSGSGSGTDFTL
]			TISSLQPDDFATYYCQQLSTYVWTFGQGTKVDI
			KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
	İ		YPREAKVQWKVDNALQSGNSQESVTEQDSKD
			STYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
			PVTKSFNRGEC*
900	948	1115	MLCGNTQLLFTVAIILLYVTCLLHWTFLHLEW
			RVSEGRHHDPLSTTLMHEKMNDN*
901	722	84	MYRLSSSMLLRALAQAMRTGHLIGQSLHSSAV
		• '	AATYKYVNKKEQESEVDMKSETDNAARILMW
			TELIRGLGMTLRYLFREPATINYPFEKGPLSPRF
			RGEHALRRYPSGEERCIACKLCEAICPAQAITIE
			AEPRADGSRRTTRYDIDMTKCIYCGFCQEACPV
			DAIVEGPNFEFSTETHEELLYNKEKLLNNGDK
002	50	250	WEAEIAANIQADYLYR*
902	1 20	259	MIELAFASFLKCASFSLLILFSFSFPLWFFLSCFA
			CSYSFSCLLSRISILSPFCHLLPRQSHDLCTNDL*

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	Sequence	deletion, \=possible nucleotide insertion
903	194	382	MSVLIWCLIFFPLEYSRPKRGLKVDNVCFSTVA
303	194	302	LSTGSRISNWSNCETCLLAEMFFLDLGFS*
904	44	1000	MAAAAVSGALGRAGWRLLQLRCLPVARCRQA
7U <del>T</del>	1 77	1000	LVPRAFHASAVGLRSSDEQKQQPPNSFSQQHSE
			TQGAEKPDPESSHSPPRYTDQGGEEEEDYESEE
			QLQHRILTAALEFVPAHGWTAEAIAEGAQSLG
			LSSAAASMFGKDGSELILHFVTQCNTRLTRVLE
	]		EEOKLVOLGOAEKRKTDOFLRDAVETRLRMLI
			PYIEHWPRALSILMLPHNIPSSLSLLTSMVDDM
			WHYAGDQSTDFNWYTRRAMLAAIYNTTELVM
			MQDSSPDFEDTWRFLENRVNDAMNMGHTAK
			QVKSTGEALVQGLMGAAVTLKNLTGLNQRR*
905	127	297	MGHLLCVWGFTYILPCISLRHSPLQPPGWEGFC
703	127	257	RNVSFPLLRASLAPHHRRKDGFI*
906	233	484	MHVLIRTPCSLILCLANSSHASLPGFSASSFLFK
700	255	101	ESCRLLINSSFLINGLEILSGAIAGQCNSFCLFSI
			SQGSLSFNASCPLP*
907	572	787	MTLLWPHTAACLSVTLYLPASSAKYFKRGEGR
			EKFITNPTTRKKKLFWRRGKRNHDQAFTGIPDQ
			VSLFPF*
908	259	552	MYLHVLVLSHRILLSPYIPSFKSVPPPVFSILQM
	Ì		APMSILDIDHPRSLGGDSSHFFSSVAQALTFCPF
	-	İ	ALRPFNNYSLQRPVFQKAPAFHHFLVKKF*
909	99	371	MFLVFCNIITVITMTSLFLILLSCIFILITCCYKCR
		İ	YISFSFTFSVTPSGFFVSILQYLAHILLLITLQFHF
			RVCYVNIITLIPLAQIFL*
910	102	278	MQLWGFLNLNFPCSSLCFWALGSRGFTLVLAV
			TPINSTGWAAHLPQHVKMRLFSIQLF*
911	142	360	MLMVLKLVICSIFIGKEGHFVISYLPSFSLNIQDT
			LKSVHQPCSALSGYNMPEKPEECSIKERHPYSQ
			RLFLE
912	191	481	MGISCKLLLLTRVCYLITPLDLERFPFPNTEQVT
			FPERRVSVFLLPLSWCLDTRLPREPGCRCRHSSP
			QDVVGGSHLVTTTLLSLPAREFWTSCIL*
913	256	393	MILFHCEKLYALRSFDFWFMLELLSTWPRALG
1			LLCPGLAIEAHEG*
914	29	265	MKTLKIFTYYFLSLSNIFILTIGLTCASGPLDFTP
			VFLLGKGSLKCKYGPVAHLPPEALESGPQIPSG
			CNWKEIPTSS*
915	79	339	MWLFCAWVSTWGQGCPPGRGQMIYASHHLSV
			HTTSPHHWLSAWALQGGAVFPELAHGASSASS
			GQADDSTCSFCSPWRVSAEHKSLT
916	57	1163	MWPALLLSHLLPLWPLLLLPLPPPAQDSSSSPR

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid		X=Unknown, *=Stop codon, /=possible nucleotide
	1	sequence	deletion, \=possible nucleotide insertion
	sequence		TPPAPARPPCARGGPSAPRHVCVWERAPPPSRS
			I i
			PRVPRSRRQVLPGTAPPATPSGFEEGPPSSQYP
			WAIVWGPTVSREDGGDPNSANPGFLDYGFAAP
			HGLATPHPNSDSMRGDGDGLILGEAPATLRPFL
			FGGRGEGVDPQLYVTITISIIIVLVATGIIFKFCW
			DRSQKRRPSGQQGALRQEESQQPLTDLSPAG
	,		VTVLGAFGDSPTPTPDHEEPRGGPRPGMPHPKG
			APAFQLNRSLSGQRFLHTLPLMCVSRPDVVVV
			CGVLTLSLMNTHPPRFRSPCMLLQRWVGGELG
			APWALIGHGLVPFHTICFSVSPSYSKDAGITLRA
			PPWEMG*
917	427	1461	MDFLVLFLFYLASVLMGLVLICVCSKTHSLKGL
			ARGGAQIFSCIIPECLQRAMHGLLHYLFHTRNH
			TFIVLHLVLQGMVYTEYTWEVFGYCQELELSL
			HYLLLPYLLLGVNLFFFTLTCGTNPGIITKANEL
			LFLHVYEFDEVMFPKNVRCSTCDLRKPARSKH
			CSVCNWCVHRFDHHCVWVNNCIGAWNIRYFL
			IYVLTLTASAATVAIVSTTFLVHLVVMSDLYQE
			TYIDDLGHLHVMDTVFLIQYLFLTFPRIVFMLG
		}	FVVVLSFLLGGYLLFVLYLAATNQTTNEWYRG
			DWAWCQRCPLVAWPPSAEPQVHRNIHSHGLR
			SNLQEIFLPAFPCHERKKQE*
918	251	538	MELVLVFLCSLLAPMVLASAAEKEKEMDPFHY
			DYQTLRIGGLVFAVVLFSVGILLILSRRCKCSFN
İ			QKPRAPGDEEAQVENLITANATEPQKAEN*
919	1355	1507	MGRRKFLPPPLLSLLSSSLPLPICHPPAPLTPGLG
			IPPCGVVGREVFSVL*
920	588	292	MRAVLLQHLFILLDRQTTKKNSNLDIGHVFREA
			LIFLADLKSQLPSVTHHQYRHLPSNWLQLLQCG
			QDKHCCLSHARLGLAQDIHSQNGLRDALMLDF
921	588	292	MRAVLLQHLFILLDRQTTKKNSNLDIGHVFREA
		1	LIFLADLKSQLPSVTHHQYRHLPSNWLQLLQCG
			QDKHCCLSHARLGLAQDIHSQNGLRDALMLDF
			*
922	288	1346	MRSLGALLLLLSACLAVSAGPVPTPPDNIQVQE
			NFNISRIYGKWYNLAIGSTCPWLKKIMDRMTV
	1		STLVLGEGATEAEISMTSTRWRKGVCEETSGA
			YEKTDTDGKFLYHKSKWNITMESYVVHTNYD
			EYAIFLTKKFSRHHGPTITAKLYGRAPQLRETLL
			QDFRVVAQGVGIPEDSIFTMADRGECVPGEQEP
		1	EPILIPRVRRAVLPQEEEGSGGGQLVTEVTKKE
			DSCQLGYSAGPCMGMTSRYFYNGTSMACETF
	<u> </u>	1	200 Q20 TOTAL ONIONTOKIT THOTOMACETE

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
ļ	sequence		OYGGCMGNGNNFVTEKECLQTCRTVAACNLPI
1			VRGPCRAFIQLWAFDAVKGKCVLFPYGGCQG
1			NGNKFYSEKECREYCGVPGDGDEELLRFSN*
923	510	1880	MFLLLPFDSLIVNLLGISLTVLFTLLLVFIIVPAIF
923	310	1000	GVSFGIRKLYMKSLLKIFAWATLRMERGAKEK
İ			NHQLYKPYTNGIIAKDPTSLEEEIKEIRRSGSSK
			ALDNTPEFELSDIFYFCRKGMETIMDDEVTKRF
			SAEELESWNLLSRTNYNFQYISLRLTVLWGLG
			VLIRYCFLLPLRIALAFTGISLLVVGTTVVGYLP
			NGRFKEFMSKHVHLMCYRICVRALTAIITYHD
			i i
			RENRPRNGGICVANHTSPIDVIILASDGYYAMV
			GQVHGGLMGVIQRAMVKACPHVWFERSEVKD
			RHLVAKRLTEHVQDKSKLPILIFPEGTCINNTSV
			MMFKKGSFEIGATVYPVAIKYDPQFGDAFWNS
			SKYGMVTYLLRMMTSWAIVCSVWYLPPMTRE
			ADEDAVQFANRVKSAIARQGGLVDLLWDGGL
024	56	1460	KREKVKDTFKEEQQKLYSKMIVGNHKDRSRS*
924	56	1459	MLLLLLPLLWGRERVEGQKSNRKDYSLTMQS
			SVTVQEGMCVHVRCSFSYPVDSQTDSDPVHGY
			WFRAGNDISWKAPVATNNPAWAVQEETRDRF
			HLLGDPQTKNCTLSIRDARMSDAGRYFFRMEK
			GNIKWNYKYDQLSVNVTALTHRPNILIPGTLES
			GCFQNLTCSVPWACEQGTPPMISWMGTSVSPL
			HPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAG
			VTTNRTIQLNVSYPPQNLTVTVFQGEGTASTAL
			GNSSSLSVLEGQSLRLVCAVDSNPPARLSWTW
			RSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQ
	1		NSLGSQHVSLNLSLQQEYTGKMRPVSGVLLGA
		1	VGGAGATALVFLSFCVIFIVVRSCRKKSARPAA
			DVGDIGMKDANTIRGSASQGNLTESWADDNPR
			HHGLAAHSSGEEREIQYAPLSFHKGEPQDLSGQ
005	ļ	1460	EATNNEYSEIKIPK*
925	56	1459	MLLLLLPLLWGRERVEGQKSNRKDYSLTMQS
			SVTVQEGMCVHVRCSFSYPVDSQTDSDPVHGY
			WFRAGNDISWKAPVATNNPAWAVQEETRDRF
			HLLGDPQTKNCTLSIRDARMSDAGRYFFRMEK
			GNIKWNYKYDQLSVNVTALTHRPNILIPGTLES
		·	GCFQNLTCSVPWACEQGTPPMISWMGTSVSPL
			HPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAG
		1	VTTNRTIQLNVSYPPQNLTVTVFQGEGTASTAL
			GNSSSLSVLEGQSLRLVCAVDSNPPARLSWTW
			RSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQ
			NSLGSQHVSLNLSLQQEYTGKMRPVSGVLLGA

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
IVO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
}	sequence	<u> </u>	VGGAGATALVFLSFCVIFIVVRSCRKKSARPAA
			DVGDIGMKDANTIRGSASQGNLTESWADDNPR
			HHGLAAHSSGEEREIQYAPLSFHKGEPQDLSGQ
		1	EATNNEYSEIKIPK*
926	167	403	MRMLLTLGGLPQMCLKFHGTPLTCPQGVPCPH
920	107	403	DSQRIQGIPKAPTGREFLAGPQRVPFPWLRSPA
		1	, , ,
927	161	415	HVRGQPSPGGPTPG MLCWKTTSGRLKDILAILLTDVLLLLQEKDQK
921	101	413	
			YVFASVDSKPPVISLQKLIVREVANEEKAMFMI
928	159	365	SASLQGPECIAAAREDPSKQ
928	139	303	MQQPEVKTWGGVVTAAMVIALAVYMGTGICG
			FLTFGAAVDPDVLLSYPSEDMAVAVARALIILS
000	1277	1007	VLTCI
929	1377	1237	MQMWWLGAQSAGRCWLRARTATSWWTCSW
020	1.504	1673	KRLVRGCCGRKTSSLVW*
930	1524	1673	MRNLSQRVTFRMVFAACSRYSRNMQPCCVLIF
00:	10.6		LKILLCLFYQSVGQFAN*
931	126	413	MSLCLAFLLHWGHFRTCPLSHVEMHLYPKRCP
			QRNAESRWSPALVHCSRHIVQVSPSSSSIEAEGS
022	10		RGSDFWGDGCLGRVLPPSIHVTSCSAETPA
932	49	615	MVPGAAGWCCLVLWLPACVAAHGFRIHDYLY
			FQVLSPGDIRYIFTATPAKDFGGIFHTRYEQIHL
]			VPAEPPEACGELSNGFFIQDQIALVERGGCSFLS
			KTRVVQEHGGRAVIISDNAVDNDSFYVEMIQD
			STQRTADIPALFLLGRDGYMIRRSLEQHGLPWA
			IISIPVNVTSIPTFELLQPPWTFW*
933	1444	1632	MACCLPCRAFPAYPTGVWPTTWLWCWAVLPI
1			PWPASWPWVCCAGPWQGWAASLCWACSVGA
			T*
934	442	143	MDWNLQFSLLLWATADISDQLFQPPQKFSWDP
			LESALCLYSSGSAKDLKGEMQSFWYPARKSPP
			LHLPALQLFYFGELPCKFLPALVVPGSTLPPSRP
			L*
935	52	309	MKITGGLLLLCTVVYFCSSSEAASLSPKKVDCSI
			YKKYPVVAIPCPITYLPVCGSDYITYGNECHLC
			TESLKSNGRVQFLHDGSC*
936	26	1057	MWAAAGGLWRSRAGLRALFRSRDAALFPGCE
			RGLHCSAVSCKNWLKKFASKTKKKVWYESPS
			LGSHSTYKPSKLEFLMRSTSKKTRKEDHARLR
	<u>.</u>		ALNGLLYKALTDLLCTPEVSQELYDLNVELSK
	i		VSLTPDFSACRAYWKTTLSAEQNAHMEAVLQ
			RSAAHMRHLLMSQQTLRNVPPIVFVQDKGNA
			ALAELDQLLAVADFGPRDERDNFVQNDFRDPD

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NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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	corresponding	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	to first amino		
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			APQPCGTTEPTTSSSLCGIDHEALNKQIMEYKR
			RKDKGLGGLVWQGQVAELTTQMQKGRKRAK
			PRLEQDSSLKSYLSGEEVEDDLDLVGAPEYECY
			APDTEELEAERGGGRTEDGHSCGASRE*
937	271	98	MTAQHHSIAVLLLNLEVTCECMEYNKVFYSGS
			FASTSFLIGYCSSSSGFYFVQPSRP*
938	140	370	MLAHLSFERSLILHLIFSGIAVSIKALTKTWMPP
			EMGSSPVYKAFSLLQCRLSAQKWGSCHSQNTL
}			HWPVWGPQTTL
939	100	411	MALLHICVGHPLLSFPKAGDFSFSSQDDPSELT
			AGAKDKEFSCLLVICLQPAPSTRSLFSWQLFLLS
			FSLVSFTLIYRGEFKKSGEAKDYLTQVQGPIDC
			GKLL
940	111	386	MFRSNPGFFFFCCCKSCILAISLGEIPRNEFTEN
1			MSLRESEDLKPDLSAFKSSALYTDVSSPVFFTY
			QNSRTLPEKPGRYCSTPVSCFSPG*
941	92	328	MCRLYSCARMPLFSTVLFSNVYINDFLLQKPEN
' ''	1-		TTSQPLSNQRVVEVAIPHVGKFMIESKEGGYDD
			EVPFTALCTIAT*
942	143	481	MGIQWTCEWPSSLSPGWKFIACLWFSMWGSRP
742	143	101	PLSQAMSHKQWPMLCSSISNPEASGTELFTYHF
			HMMGYIERFWPTEELAQRCSLHKELPCTVFTE
			KHCSCTFLMVFGVCT*
943	956	1558	MQGMKTQLIQLSTLLRLLDSGFCSYLESQDSGY
743	930	1336	LYFCFRWLLIRFKREFSFLDILRLWEVMWTELP
			CTNFHLLLCCAILESEKQQIMEKHYGFNEILKHI
			NELSMKIDVEDILCKAEAISLQMVKCKELPQAV
		1	CEILGLQGSEVTTPDSDVGEDENVVMTPCPTSA
			FOSNALPTLSASGARNDSPTQIPVSSDVCRLTPA
			*
044	122	210	MGASLALGFTEVVLVLGFTVKLGAHLTLLPPL
944	23	319	
			GGHLSPYCAAQAWEGVKQLMCNCSSYPLQCII CCIYATPGCYNLSFGILSSCEGIFVYEWLFEMLL
			CCITATPGCTNLSFGILSSCEGIFVTEWLFEMILL
			<u> </u>

## WHAT IS CLAIMED IS:

- 1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:1-236 and 473-708, a mature protein coding portion of SEQ ID NO:1-236 and 473-708, an active domain coding portion of SEQ ID NO:1-236 and 473-708, and complementary sequences thereof.
- 2. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide hybridizes to the polynucleotide of claim 1 under stringent hybridization conditions.
- 3. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide has greater than about 90% sequence identity with the polynucleotide of claim 1.
- 4. The polynucleotide of claim 1 wherein said polynucleotide is DNA.
- 5. An isolated polynucleotide of claim 1 wherein said polynucleotide comprises the complementary sequences.
- 6. A vector comprising the polynucleotide of claim 1.
- 7. An expression vector comprising the polynucleotide of claim 1.
- 8. A host cell genetically engineered to comprise the polynucleotide of claim 1.
- 9. A host cell genetically engineered to comprise the polynucleotide of claim 1 operatively associated with a regulatory sequence that modulates expression of the polynucleotide in the host cell.
- 10. An isolated polypeptide, wherein the polypeptide is selected from the group consisting of:

(a) a polypeptide encoded by any one of the polynucleotides of claim 1; and

- (b) a polypeptide encoded by a polynucleotide hybridizing under stringent conditions with any one of SEQ ID NO:1-236 and 473-708.
- 11. A composition comprising the polypeptide of claim 10 and a carrier.
- 12. An antibody directed against the polypeptide of claim 10.
- 13. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form the complex; and
- b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected.
- 14. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- a) contacting the sample under stringent hybridization conditions with nucleic acid primers that anneal to the polynucleotide of claim 1 under such conditions;
- b) amplifying a product comprising at least a portion of the polynucleotide of claim 1; and
- c) detecting said product and thereby the polynucleotide of claim 1 in the sample.
- 15. The method of claim 14, wherein the polynucleotide is an RNA molecule and the method further comprises reverse transcribing an annealed RNA molecule into a cDNA polynucleotide.
- 16. A method for detecting the polypeptide of claim 10 in a sample, comprising:

 a) contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex; and

- b) detecting formation of the complex, so that if a complex formation is detected, the polypeptide of claim 10 is detected.
- 17. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
- a) contacting the compound with the polypeptide of claim 10 under conditions sufficient to form a polypeptide/compound complex; and
- b) detecting the complex, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.
- 18. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
- a) contacting the compound with the polypeptide of claim 10; in a cell, under conditions sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and
- b) detecting the complex by detecting reporter gene sequence expression, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.
- 19. A method of producing the polypeptide of claim 10, comprising,
- a) culturing a host cell comprising a polynucleotide sequence selected from the group consisting of a polynucleotide sequence of SEQ ID NO:1-236 and 473-708, a mature protein coding portion of SEQ ID NO:1-236 and 473-708, an active domain coding portion of SEQ ID NO:1-236 and 473-708, complementary sequences thereof and a polynucleotide sequence hybridizing under stringent conditions to SEQ ID NO:1-236 and 473-708, under conditions sufficient to express the polypeptide in said cell; and
  - b) isolating the polypeptide from the cell culture or cells of step (a).

20. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of any one of the polypeptides SEQ ID NO:237-472 and 709-944, the mature protein portion thereof, or the active domain thereof.

- 21. The polypeptide of claim 20 wherein the polypeptide is provided on a polypeptide array.
- 22. A collection of polynucleotides, wherein the collection comprising the sequence information of at least one of SEQ ID NO:1-236 and 473-708.
- 23. The collection of claim 22, wherein the collection is provided on a nucleic acid array.
- 24. The collection of claim 23, wherein the array detects full-matches to any one of the polynucleotides in the collection.
- 25. The collection of claim 23, wherein the array detects mismatches to any one of the polynucleotides in the collection.
- 26. The collection of claim 22, wherein the collection is provided in a computerreadable format.
- 27. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.
- 28. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising an antibody that specifically binds to a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.

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ttt Phe	cca Pro	gtt Val	atc Ile	ttg Leu 320	ggt Gly	act Thr	cac His	tta Leu	ccc Pro 325	ttc Phe	ttt Phe	att Ile	cat His	ggc Gly 330	tgc Cys	1852

						tac Tyr										1900
						atg Met										1948
						tgt Cys 370										1996
						aaa Lys										2044
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						ttt Phe										2188
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-		-				aaa Lys	-				_	-	_	-	-	2284
						aac Asn				_				_	_	2332
-		_				ttg Leu				_		_	_		_	2380
						tca Ser										2428
ttc Phe	cac His 525	act Thr	cac His	ttg Leu	cca Pro	gag Glu 530	ggt Gly	cga Arg	att Ile	gga Gly	agt Ser 535	cac His	ata Ile	tat Tyr	gtc Val	2476
tat Tyr 540	gaa Glu	cgg Arg	aag Lys	tta Leu	aaa Lys 545	GJA aaa	aaa Lys	ttc Phe	aac Asn	atg Met 550	aag Lys	atg Met	aaa Lys	ttc Phe	tga	2524
act	ttcc	tag	ataa	atta	ac a	ttgc	tggg	t gg	aaat	attc	aga	tgct	gct	taaa	tacttc	2584
ggt	aaac	act	gggt	aaga	tt c	atgg	aact	t ag	aaaa	aagc	tgt	atga	act	gctt	taccaa	2644
ata	tcac	tac	tgag	gaaa	tg t	ataa	aata	c ca	cata	gtat	aaa	atta	cat	gtta	atacaa	2704
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		-														
	gtg Val															683
gtg Val	cag Gln	gtg Val 210	ggc Gly	tat Tyr	ggt Gly	atg Met	gct Ala 215	gca Ala	gjå aaa	tac Tyr	acc Thr	atc Ile 220	ttc Phe	atc Ile	acc Thr	731
	ttc Phe 225															779
atg Met 240	atc Ile	atg Met	att Ile	gly ggg	atg Met 245	gtc Val	tcc Ser	ttt Phe	Gly 333	tca Ser 250	gga Gly	gcc Ala	ctc Leu	ctc Leu	ttg Leu 255	827
-	ttt Phe	-					_				_	_	-	_	_	875
_	ttt Phe	-				_				_		_	_			923
	ata Ile	_						_			_		_	_	-	971
	ttg Leu 305															1019
	cag Gln			_	_						_		_			1067
	ttt Phe															1115
	caa Gln	-		_					-					tga *	aga	1163
tgc	ttac	ctg	cagg	aact	ga a	aaca	tcag	c ca	tggc	cagg	ccc	ccag	aag	acaa	aagaag	1223
gga	ccgg	gga	actg	gtga	cc t	aagc	aacc	c ac	tgct	t						1260

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			tat Tyr													197
			aaa Lys													245
aat Asn 70	Ile	aaa Lys	gta Val	acc Thr	tta Leu 75	ggt Gly	gct Ala	cac His	aat Asn	atc İle 80	aag Lys	aaa Lys	caa Gln	gaa Glu	aac Asn 85	293
acc Thr	cag Gln	gtt Val	atc Ile	tct Ser 90	gtt Val	gta Val	aaa Lys	gcc Ala	aaa Lys 95	cct Pro	cac His	gag Glu	aac Asn	tat Tyr 100	gac Asp	341
			cat His 105													389
			aat Asn													437
gac Asp	tgg Trp 135	gtg Val	aaa Lys	cct Pro	gly aaa	cag Gln 140	gtg Val	tgc Cys	aca Thr	gtg Val	gca Ala 145	ggt Gly	tgg Trp	gga Gly	cgc Arg	485
ttg Leu 150	gcc Ala	aat Asn	tgt Cys	act Thr	tcg Ser 155	tct Ser	aac Asn	aca Thr	ctt Leu	caa Gln 160	gaa Glu	gtg Val	aat Asn	cta Leu	gaa Glu 165	533
gtt Val	cag Gln	aaa Lys	ggc Gly	cag Gln 170	aag Lys	tgc Cys	caa Gln	gac Asp	atg Met 175	tcc Ser	gaa Glu	gac Asp	tac Tyr	aac Asn 180	gac Asp	581
tcc Ser	atc Ile	cag Gln	ctt Leu 185	tgt Cys	gtg Val	gga Gly	aac Asn	ccc Pro 190	agc Ser	gag Glu	ggg ggg	aag Lys	gct Ala 195	act Thr	ggt Gly	629
aag Lys	gga Gly	gac Asp 200	tca Ser	gly ggg	ggt Gly	ccc Pro	ttt Phe 205	gtg Val	tgc Cys	gat Asp	gga Gly	atg Met 210	gcc Ala	cca Pro	gly aaa	67 <b>7</b>
cat His	tgg Trp 215	cag Gln	tta Leu	tcg Ser	gct Ala	tgg Trp 220	gta Val	ctg Leu	gga Gly	aca Thr	ctt Leu 225	tct Ser	cga Arg	gaa Glu	ttt Phe	725
ccc Pro 230	cag Gln	aat Asn	ctc Leu	cag Gln	ctt Leu 235	tta Leu	tac Tyr	cgg Arg	gga Gly	ttt Phe 240	aga Arg	aaa Lys	cca Pro	atg Met	aaa Lys 245	773
ggc Gly	cct Pro	taa *	caat	tcc	taga	aacc	ca a	aacc	ctgg	g to	ttgc	ggcc	aat	ggcc	cca	829

889

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WO 01/55437				PCT/US01/02623
	160	16	5	170
Thr Gly Gly I			g ggt ccc tct ggt t Gly Pro Ser Gly 185	•
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	lu Pro Gly G		t tca ggt ccc atg a Ser Gly Pro Met 215	
			gga gat gat ggg n Gly Asp Asp Gly 230	
gga aaa cct g Gly Lys Pro G	gt cgt cct g lly Arg Pro G 240	gt gag cgt ggg ly Glu Arg Gly 245	g cet cet ggg cet y Pro Pro Gly Pro	cag ggt 892 Gln Gly 250
Ala Arg Gly L			c cct gga atg aag 1 Pro Gly Met Lys 265	
			g gga gat gct ggt s Gly Asp Ala Gly 280	
ggt cct aag g Gly Pro Lys G 285	ly Glu Pro G	gc agc cct ggt ly Ser Pro Gl <sub>l</sub> 90	gaa aat gga gct Glu Asn Gly Ala 295	cct ggt 1036 Pro Gly
cag atg ggc c Gln Met Gly P 300	cc cgt ggc c ro Arg Gly L 305	eg oot ggt gag eu Pro Gly Glu	g aga ggt cgc cct 1 Arg Gly Arg Pro 310	gga gcc 1084 Gly Ala 315
			ggt gct act ggt Gly Ala Thr Gly	
Gly Pro Pro G	gt ccc acc g ly Pro Thr G 35	ge eee get ggt ly Pro Ala Gly 340	c dct cct ggc ttc Pro Pro Gly Phe 345	cct ggt 1180 Pro Gly
gct gtt ggt g Ala Val Gly A 350	ct aag ggt g la Lys Gly G	aa get ggt eed lu Ala Gly Pro 355	c caa ggg ccc cga o Gln Gly Pro Arg 360	ggc tct 1228 Gly Ser
gaa ggt ccc c Glu Gly Pro G 365	ln Gly Val A	gt ggt gag cet gg Gly Glu Pro 70	ggc ccc cct ggc Gly Pro Pro Gly 375	cct gct 1276 Pro Ala
ggt gct gct g Gly Ala Ala G 380	gc cet get ge ly Pro Ala G 385	ga aac cct ggt .y Asn Pro Gly	gct gat gga cag Ala Asp Gly Gln 390	cct ggt 1324 Pro Gly 395
gct aaa ggt g Ala Lys Gly A	cc aat ggt go la Asn Gly Ai 400	et cct ggt att a Pro Gly Ile 405	gct ggt gct cct e Ala Gly Ala Pro	ggc ttc 1372 Gly Phe 410
cct ggt gcc c Pro Gly Ala A	ga ggc ccc to rg Gly Pro Se	t gga ccc cag r Gly Pro Gln	ggc ccc ggc ggc (	cct cct 1420 Pro Pro

415 420 425

			415					420					425			
ggt Gly	ccc Pro	aag Lys 430	ggt Gly	aac Asn	agc Ser	Gly	gaa Glu 435	cct Pro	ggt Gly	gct Ala	cct Pro	ggc Gly 440	agc Ser	aaa Lys	gga Gly	1468
gac Asp	act Thr 445	ggt Gly	gct Ala	aag Lys	gga Gly	gag Glu 450	cct Pro	ggc Gly	cct Pro	gtt Val	ggt Gly 455	gtt Val	caa Gln	gga Gly	ccc Pro	1516
cct Pro 460	ggc Gly	cct Pro	gct Ala	gga Gly	gag Glu 465	gaa Glu	gga Gly	aag Lys	cga Arg	gga Gly 470	gct Ala	cga Arg	ggt Gly	gaa Glu	ccc Pro 475	1564
gga Gly	ccc Pro	act Thr	ggc Gly	ctg Leu 480	ccc Pro	gga Gly	ccc Pro	cct Pro	ggc Gly 485	gag Glu	cgt Arg	ggt Gly	gga Gly	cct Pro 490	ggt Gly	1612
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ctg Leu 540	act Thr	gga Gly	ago Ser	cct Pro	ggc Gly 545	agc Ser	cct Pro	ggt Gly	cct Pro	gat Asp 550	Gly	aaa Lys	act Thr	ggc	ccc Pro 555	1804
ect Pro	ggt Gly	ccc Pro	gcc Ala	ggt Gly 560	Gln	gat Asp	ggt Gly	cgc Arg	ccc Pro 565	Gly	ccc Pro	cca Pro	Gly	cca Pro 570	Pro	1852
ggt Gly	gcc	e cgt Arg	ggt Gly 575	, Gln	gct Ala	ggt Gly	gtg Val	atg Met 580	Gly	ttc Phe	cct Pro	gga Gly	cct Pro 585	Lys	ggt	1900
gct Ala	gct Ala	gga Gl <sub>3</sub> 590	y Glu	g ccc u Pro	ggc gly	aag Lys	gct Ala 595	Gly	gag Glu	cga Arg	ggt Gly	gtt Val 600	Pro	gga Gly	ccc Pro	1948
cct	ggc Gly 605	/ Ala	t gto a Val	c ggt l Gly	cct Pro	gct Ala 610	Gly	aaa / Lys	gat Asp	gga Gly	gag Glu 619	ı Ala	gga Gly	gct Ala	cag Gln	1996
gga Gly 620	Pro	o pro	t gge o Gl	c cct y Pro	gct Ala 625	a Gly	ccc Pro	c gct o Ala	ggo Gly	gag Glu 630	ı Arç	ggt Gly	gaa Glu	a caa 1 Glr	ggc Gly 635	2044
ect Pro	gct Ala	gg a Gl	c tc y Se	c cco r Pro 640	o Gly	a tto y Phe	caç Glr	g ggt n Gly	Cto Let 649	ı Pro	t ggt o Gly	cct Pro	gct Ala	ggt a Gly 650	cct Pro	2092
cca Pro	a ggt o Gly	t ga y Gl	a gc u Al 65	a Gl	c aaa y Lys	a cct s Pro	ggt Gly	t gaa y Glu 660	ı Glı	g ggt n Gly	t gti y Val	t cct l Pro	gg 66!	y Ası	c ctt p Leu	2140
gg Gl	gc Ala	c cc a Pr	t gg o Gl	c cc y Pr	c tci o Se:	t gga r Gly	.gca / Ala	a aga a Arq	a ggo	gaq y Gl	g aga u Ar	a ggi g Gl	t tto y Pho	e er	ggc Gly	2188

670 . 675 . 680

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											aaa Lys					2428
ggt Gly	ctg Leu 765	acc Thr	ggc Gly	ccc Pro	att Ile	ggt Gly 770	cct Pro	cct Pro	ggc Gly	cct Pro	gct Ala 775	ggt Gly	gcc Ala	cct Pro	ggt Gly	2476
											ggt Gly					2524
											ccc Pro					2572
		_					_	_			cct Pro					2620
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											aat Asn 855					2716
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			_	_		_	_				ggc Gly					2812
_									_		aaa Lys	-				2860
		-						-		-	cct Pro		-	_		2908
							-				gga Gly				-	2956

925 930 935

	•																
gat Asp 940	ggt Gly	cct Pro	gct Ala	ggt Gly	gct Ala 945	cct Pro	ggt Gly	act Thr	ccc Pro	950 950	cct Pro	caa Gln	ggt Gly	att Ile	gct Ala 955	3	3004
gga Gly	cag Gln	cgt Arg	ggt Gly	gtg Val 960	gtc Val	ggc Gly	ctg Leu	cct Pro	ggt Gly 965	cag Gln	aga Arg	gga Gly	gag Glu	aga Arg 970	ggc Gly	3	3052
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Gly	ttg Leu 1005	gct Ala	gga Gly	ccc Pro	Pro	ggt Gly 1010	gaa Glu	tct Ser	gga Gly	Arg	gag Glu 1015	Gly ggg	gct Ala	cct Pro	ggt Gly		3196
gcc Ala 1020	gaa Glu	ggt Gly	tcc Ser	Pro	gga Gly 1025	cga Arg	gac Asp	ggt Gly	Ser	cct Pro 1030	ggc Gly	gcc Ala	aag Lys	Gly	gac Asp 1035		3244
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		Pro			Pro		Gly	ccc Pro		Gly							3436
	Glu	_		Asp	-	Gly		aag Lys	Gly		Arg			Ser			3484
Leu	Gln	Gly	Pro	Pro 1120	Gly	Pro	Pro		Ser 1125	Pro	Gly	Glu	Gln	Gly 1130	Pro		3532
				Gly				ccc Pro 1140				Pro		Ser			3580
	Ala		Gly		_			aac Asn			Pro		Pro				3628
		Gly		-	Gly	_	Thr	ggt		Ala		Pro					3676
								ccc Pro							ggt Gly		3724

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Gly Gly Arg	tac tac cgg gct gat gat g Tyr Tyr Arg Ala Asp Asp i 1215 1220	gcc aat gtg gtt cgt gad Ala Asn Val Val Arg Asp 1225	c cgt 3820 o Arg
gac ctc gag Asp Leu Glu 1230	gtg gac acc acc ctc aag a Val Asp Thr Thr Leu Lys ! 1235	agc ctg agc cag cag ato Ser Leu Ser Gln Gln Ilo 1240	gag 3868 Glu
aac atc cgg Asn Ile Arg 1245	agc cca gag ggc agc cgc a Ser Pro Glu Gly Ser Arg 1 1250	aag aac ccc gcc cgc acc Lys Asn Pro Ala Arg Th 1255	c tgc 3916 c Cys
cgt gac ctc Arg Asp Leu 1260	aag atg tgc cac tct gac Lys Met Cys His Ser Asp 1265	tgg aag agt gga gag ta Trp Lys Ser Gly Glu Ty: 1270	e tgg 3964 c Trp 1275
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gcc cag aag Ala Gln Lys 1310	aac tgg tac atc agc aag Asn Trp Tyr Ile Ser Lys 1315	aac ccc aag gac aag ag Asn Pro Lys Asp Lys Ar 1320	g cat 4108 g His
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aac agc gtg Asn Ser Val	gcc tac atg gac cag cag Ala Tyr Met Asp Gln Gln 1375 1380	act ggc aac ctc aag aa Thr Gly Asn Leu Lys Ly 1385	g gcc 4300 s Ala
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50

845

Ala Thr Ile Leu Asp Leu Ser Cys Asn Lys Leu Thr Thr Leu Pro Ser

gat the tgt gge etc aca cae etg gtg aag eta gae etg agt aag aad

45

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cac His	ctg Leu 90	gat Asp	ctc Leu	ctc Leu	aac Asn	aac Asn 95	aag Lys	ctg Leu	gtc Val	acc Thr	ttg Leu 100	cct Pro	gtc Val	agc Ser	ttt Phe	941
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tgt Cys	aag Lys	cag Gln	tgt Cys 140	gca Ala	aac Asn	aag Lys	gtg Val	tta Leu 145	cag Gln	cac His	atg Met	aag Lys	gcc Ala 150	gtg Val	cag Gln	1085
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_	Cys				gag Glu 270	Leu	-	-	-		Leu	_				1469
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atg acc cag aac tac cag gac tca cca acc ctc cag gct ccc aga gga Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala Pro Arg Gly 200 205 210	800
agg gcc agc gag ccc aag cac aaa acc agg cag aga tag ctgcctgcta Arg Ala Ser Glu Pro Lys His Lys Thr Arg Gln Arg * 215 220	849
gatageegge tttgecatee gggeatgtgg ceacactget caccacegae gatgtgggta	909
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cga cgc tcc ttc tgg act gta atg cgc act gcg tgg aga tgt tcg tgt
Arg Arg Ser Phe Trp Thr Val Met Arg Thr Ala Trp Arg Cys Ser Cys

5 10 15

tcc agt gta gac agg gcg ttg tca cat cag gca gga cta cag gga caa 212 Ser Ser Val Asp Arg Ala Leu Ser His Gln Ala Gly Leu Gln Gly Gln 20 25 30

tgt ttg tca gcc tgt ctt ctg ggc aac ttg ggg tat cct ccc ttt ata 260
Cys Leu Ser Ala Cys Leu Leu Gly Asn Leu Gly Tyr Pro Pro Phe Ile
35 40 45

tea cet cet gee cag gtg ete tge gee gee aga gea tea tgt eat ttg

Ser Pro Pro Ala Gln Val Leu Cys Ala Ala Arg Ala Ser Cys His Leu

50 65

gga tcc ctg atg gca att ttg aga ctt tgg ttc aca gta aag att ggt 356 Gly Ser Leu Met Ala Ile Leu Arg Leu Trp Phe Thr Val Lys Ile Gly 70 75 80

cct gtg tga tcttaaa gtaatgtggc ttaaaaacaa atggctgtca gggaattgta 412 Pro Val \*

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24

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gta Val	aag Lys	gta Val	att Ile 220	gaa Glu	aaa Lys	aaa Lys	ctc Leu	gcc Ala 225	att Ile	tgg Trp	gag Glu	cag Gln	ctg Leu 230	tct Ser	cca Pro	2103

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we	O 01/5	5437												]	PCT/US01/0	2623
Phe	Ser 35	Val	Ser	Pro	Gly	Gly 40	Thr	Val	Thr	Leu	Thr 45	Cys	Gly	Leu	Asn	
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			cct Pro													296
			tct Ser 85													344
			atc Ile													392
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			gtc Val													488
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			aac Asn													680
			tgg Trp													728
gaa Glu	Gly ggg	agc Ser	acc Thr	gtg Val 230	gag Glu	aag Lys	aca Thr	gtg Val	gcc Ala 235	cct Pro	aca Thr	gaa Glu	tgt Cys	tca Ser 240	tag *	776
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34

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Ala Pro Gly Arg Thr Met Val Pro Leu Val Pro Ala Leu Val Met Leu

10
15
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ggg aag aaa gtc agc tcc cag cgc ttc gag gtc att gag ttt gat gat 593 Gly Lys Lys Val Ser Ser Gln Arg Phe Glu Val Ile Glu Phe Asp Asp 70 75 80 85

ggg gca ggg tca gtg ctt cgg atc cag cca ttg cgg gtg cag cga gat 641 Gly Ala Gly Ser Val Leu Arg Ile Gln Pro Leu Arg Val Gln Arg Asp 90 95 100

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ttc Phe	ccc Pro	caa Gln 920	aac Asn	ctg Leu	cat His	gtg Val	aca Thr 925	gga Gly	ctg Leu	acc Thr	acg Thr	tct Ser 930	acc Thr	aca Thr	gaa Glu	3137
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agc Ser 950	tac Tyr	acc Thr	gtg Val	gtg Val	ttc Phe 955	cga Arg	gac Asp	atc Ile	aac Asn	agc Ser 960	caa Gln	cag Gln	gag Glu	ctg Leu	cag Gln 965	3233
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ctc Leu 1030	agc Ser	tgg Trp	gag Glu	Val	ccc Pro 1035	gac Asp	tcc Ser	tat Tyr	Lys	tca Ser 1040	Ala	gtg Val	ccc Pro	Phe	aag Lys 1045	3473
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Arg	aca Thr 1095	Ala	e ccc Pro	gac Asp	cto Leu	ctg Leu 1100	Pro	cac His	aag Lys	Pro	ctg Leu 1105	Pro	gcc Ala	tct Ser	gcc Ala	3665
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PCT/US01/02623 WO 01/55437 Asp Gly Val Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Asp Gly 1405 tac ege aag cag aat gee tac ate gee aeg cag gge eec etg eec gag 4625 Tyr Arg Lys Gln Asn Ala Tyr Ile Ala Thr Gln Gly Pro Leu Pro Glu 1420 acc atg ggc gat ttc tgg aga atg gtg tgg gaa cag cgc acg gcc act 4673 Thr Met Gly Asp Phe Trp Arg Met Val Trp Glu Gln Arg Thr Ala Thr 1440 1435 1430 gtg gtc atg atg aca cgg ctg gag gag aag tcc cgg gta aaa tgt gat 4721 Val Val Met Met Thr Arg Leu Glu Glu Lys Ser Arg Val Lys Cys Asp 1450 cag tac tgg cca gcc cgt ggc acc gag acc tgt ggc ctt att cag gtg 4769 Gln Tyr Trp Pro Ala Arg Gly Thr Glu Thr Cys Gly Leu Ile Gln Val 1465 acc ctg ttg gac aca gtg gag ctg gcc aca tac act gtg cgc acc ttc 4817 Thr Leu Leu Asp Thr Val Glu Leu Ala Thr Tyr Thr Val Arg Thr Phe 1485 1480 gca ctc cac aag agt ggc tcc agt gag aag cgt gag ctg cgt cag ttt 4865 Ala Leu His Lys Ser Gly Ser Ser Glu Lys Arg Glu Leu Arg Gln Phe 1505 1495 cag ttc atg gcc tgg cca gac cat gga gtt cct gag tac cca act ccc 4913 Gln Phe Met Ala Trp Pro Asp His Gly Val Pro Glu Tyr Pro Thr Pro 1520 1515 1510 ate ctg gcc ttc cta cga cgg gtc aag gcc tgc aac ccc cta gac gca 4961 Ile Leu Ala Phe Leu Arg Arg Val Lys Ala Cys Asn Pro Leu Asp Ala 1535 1530 ggg ccc atg gtg gtg cac tgc agc gcg ggc gtg ggc cgc acc ggc tgc 5009 Gly Pro Met Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Cys 1550 1545 ttc atc gtg att gat gcc atg ttg gag cgg atg aag cac gag aag acg 5057 Phe Ile Val Ile Asp Ala Met Leu Glu Arg Met Lys His Glu Lys Thr 1565 1560 gtg gac atc tat ggc cac gtg acc tgc atg cga tca cag agg aac tac 5105 Val Asp Ile Tyr Gly His Val Thr Cys Met Arg Ser Gln Arg Asn Tyr 1585 1580 atg gtg cag acg gag gac cag tac gtg ttc atc cat gag gcg ctg ctg 5153 Met Val Gln Thr Glu Asp Gln Tyr Val Phe Ile His Glu Ala Leu Leu 1600 1595 gag gct gcc acg tgc ggc cac aca gag gtg cct gcc cgc aac ctg tat 5201 Glu Ala Ala Thr Cys Gly His Thr Glu Val Pro Ala Arg Asn Leu Tyr 1615 gee cac ate cag aag etg gge caa gtg eet eea ggg gag agt gtg ace 5249 Ala His Ile Gln Lys Leu Gly Gln Val Pro Pro Gly Glu Ser Val Thr 1630 gec atg gag etc gag ttc aag ttg etg gec age tee aag gec eac aeg 5297 Ala Met Glu Leu Glu Phe Lys Leu Leu Ala Ser Ser Lys Ala His Thr 1640 tee ege tte ate age gee aac etg eec tge aac aag tte aag aac egg 5345

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aag ggc tcc Lys Gly Se:	c caa acg gcc cca ctc gac ggc tca ccg gag gat ggt cct r Gln Thr Ala Pro Leu Asp Gly Ser Pro Glu Asp Gly Pro 20 25	216
	g gtg ttt gtt gaa cag ata aga gac aac aaa aca gac taa p Val Phe Val Glu Gln Ile Arg Asp Asn Lys Thr Asp  * 35	264
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694

1031

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47

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tactcattct aggactaatg atgatggtaa agaagttgcc agtgttatgg caatgaaaat	240
ttcagaaagg aggagttgat gatcttctag atg tat atg aac acc tgt cta Met Tyr Met Asn Thr Cys Leu 1 5	291
tat ctg cat gta tat gtt ttg acc tgc agt ggt tgc aat gtt gat atg Tyr Leu His Val Tyr Val Leu Thr Cys Ser Gly Cys Asn Val Asp Met 10 15 20	339
tgt tca aga tta ttc ctg tct aca aaa ctg aag gcc cat gtt caa att Cys Ser Arg Leu Phe Leu Ser Thr Lys Leu Lys Ala His Val Gln Ile 25 30 35	387
gtt ctt tat tgg gtg ttt tta tgg tca cgt ggt aac aat ttt ctt acc Val Leu Tyr Trp Val Phe Leu Trp Ser Arg Gly Asn Asn Phe Leu Thr 40 45 50	435
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ctt ggc ata tta tat gat gca att ttt tat tgc ttt gtc cat gca ata	155

ļ

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Leu Gly Ile Leu Tyr Asp Ala Ile Phe Tyr Cys Phe Val His Ala Ile 15 20 25 30	
aac gct gat aaa ttt ttc ggt tta aaa ttt acc aag tct gct act gta Asn Ala Asp Lys Phe Phe Gly Leu Lys Phe Thr Lys Ser Ala Thr Val 35 40 45	203
tcc cag aat tct caa tga aagaaa atatttacag tttttaacat tacaggtaga Ser Gln Asn Ser Gln * 50	257
aaaaggatca aagtgatttt ottattttto tatotaatto atggaaaaaa gaacacaggo	317
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tac gat ttt ctt ttg ctc ttg agt ttt att ttc ata gtg gca tct tac Tyr Asp Phe Leu Leu Leu Ser Phe Ile Phe Ile Val Ala Ser Tyr 5 10 15	163
tgg tct ttc ctt tcc acc ata ttt ttg gat gtt gtg tgt tcc att tta Trp Ser Phe Leu Ser Thr Ile Phe Leu Asp Val Val Cys Ser Ile Leu 20 25 30	211
cat tgc cca gtt aaa cca cag aca ctc ctg aag tca tgt tta cat gtg His Cys Pro Val Lys Pro Gln Thr Leu Leu Lys Ser Cys Leu His Val 35 40 45	259
gac tgc aag tca acc tag ttggca tgttgatcta agctacaaat tgcactgctg Asp Cys Lys Ser Thr * 50 55	313
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	cag Gln 85	taa *	gcts	ggcc	aac	agaag	get g	gacto	catgo	ee e	ccaa	accc	c ac	catao	caga	1013
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                                                                     117
                                                     Met Lys Pro
                                                       1
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Tyr Cys Met Tyr Pro Phe Leu Ser Gly Leu Leu Ser Ser Leu Leu Phe
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														tat Tyr 50			261
					_	_				att Ile				gact	tatt		310
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ctaa	agaga	agg a	aattt	gtag	gg to	catag	ggata	a tg	tgtai	tgat	cago	cttgg	ggt .	ataca	actac	c	430
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Tyr Ser Tyr Met Val Phe Ser Val Asn Leu Tyr Lys \* 55 60 65

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1 5 10

ttc aca ggc ccg gat tgt cgt ttt gtg aat ttt aaa aaa ggt gat cct
Phe Thr Gly Pro Asp Cys Arg Phe Val Asn Phe Lys Lys Gly Asp Pro

gta tat gtt tac tat aaa ctg gca aga gga tgg cct gaa gtt tgg gct 265 Val Tyr Val Tyr Tyr Lys Leu Ala Arg Gly Trp Pro Glu Val Trp Ala 30 35 40

25

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gta gtt cat gaa tat acc aaa gaa gag cta caa gtt cca aca gat gag
Val Val His Glu Tyr Thr Lys Glu Glu Leu Gln Val Pro Thr Asp Glu
60 70 75

aat gta gaa gaa ctt tta ggg ttt ttg gaa ctg tac aat tct gca gct 457 Asn Val Glu Glu Leu Gly Phe Leu Glu Leu Tyr Asn Ser Ala Ala 95 100 105

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gcc aac tca gag gaa agt gat Ala Asn Ser Glu Glu Ser Asp 140 145	agt gta ttc tca Ser Val Phe Ser 150	Glu Asn Thr Glu A	at 603 sp 55
ctt cag gaa cag ttt aca act Leu Gln Glu Gln Phe Thr Thr 160	tca aag cac cac Ser Lys His His 165	tcc cat ggc aac a Ser His Gly Asn A 170	gg 649 rg
caa gca aat tat gct tca gga Gln Ala Asn Tyr Ala Ser Gly 175			
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cataagtett aggteteeaa aggad	cggaa aagaatgatg	gctattaact tttgaa	aaaa 81
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cgg ggt gga gga gtt aat ttt Arg Gly Gly Gly Val Asn Phe 20	Gly Glu Lys Asp	gca aaa gtc ccc gg Ala Lys Val Pro G 30	gg 212 ly
acc tgg aga gat gga gtc agg Thr Trp Arg Asp Gly Val Arg 35 40	gtc cct gga gaa Val Pro Gly Glu 45	Gly Ala Ser Trp As	ac 260 sp 50
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65 70

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Met Arg Gln Ile
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Ala Val Phe Gln Arg Phe Met Phe Pro Phe Leu Leu Pro Trp Leu Ser
5 10 15 20

tgc att ttt agc tcc agt caa aat tct att tat tat gta tca act ttt

392
Cys Ile Phe Ser Ser Ser Gln Asn Ser Ile Tyr Tyr Val Ser Thr Phe

25
30
35

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Asn Ala Lys Lys Ser Cys Gln Lys Tyr Leu Ser Ser Leu Lys Leu Ser  15 20 25	130
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Thr Leu Leu Ser Pro Leu Leu Phe Leu Pro Phe Tyr Thr Pro Ser Leu 30 35 40	
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Lys Gly Trp Gly Ile Phe Val Leu Ser Phe Tyr Phe Met Leu Ile Ile 45 50 55 60	
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Ala Asp Cys Asn Leu Phe Lys Ile Ile Ile * 65 70	
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wo	VO 01/55437														PCT/US01/02623		
				85					90					95			
	_			_									gag Glu				396

105

tgg tgt cgc ggc ggc gcc tac cta gtg gct ttc tcg ctt cgc gtg gag

Trp Cys Arg Gly Gly Ala Tyr Leu Val Ala Phe Ser Leu Arg Val Glu

115 120 125

110

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Arg Cys Ser Asp Gly Glu Glu Leu Gln Gly Pro Gly Leu Ser Trp Gly
145 150 155 160

gac ttt gga gac tgg agt gac cat tgc ccc aag ggc gcg tgc ggc ctg 588
Asp Phe Gly Asp Trp Ser Asp His Cys Pro Lys Gly Ala Cys Gly Leu
165 170 175

cag acc aag atc cag gga cct aga ggc ctc ggc gat gac act gcg ctg 636 Gln Thr Lys Ile Gln Gly Pro Arg Gly Leu Gly Asp Asp Thr Ala Leu 180 185 190

aac gac gcg cgc tta ttc tgc tgc cgc agt tga acggcgcc gtcgccgccg 687 Asn Asp Ala Arg Leu Phe Cys Cys Arg Ser \*

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caa gaa gtg aac ata acc tgt agc cac aac aat gct aca aat gat 144 Gln Glu Val Asn Ile Thr Cys Ser His Asn Asn Ile Ala Thr Asn Asp

tat atc acg tgg tac caa cag ttt ccc agc caa gga cca cga ttt att

Tyr Ile Thr Trp Tyr Gln Gln Phe Pro Ser Gln Gly Pro Arg Phe Ile

50 55 60

att caa gga tac aag aca aaa gtt aca aac gaa gtg gcc tcc ctg ttt 240

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115.

tta gcc cgc agg ggg ctg cgc ttc tga cagcc taaccccatt cctgtgcgga Leu Ala Arg Arg Gly Leu Arg Phe \* 125 cagecettee teccatttee cattaaagag ceagtttatt ttetaaaaaa aaaa 493 <210> 34 <211> 1900 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (314)..(709) <220> <221> misc\_feature <222> (1) ... (1900) <223> n = a,t,c or g<400> 34 60 atttggccct cgaggccaag aattcggcac gagcataagg ttgtagtagc aggagccctc tatettttgt tegggnneat ggaaggggte eteanagenn nngagaetea gaetgatett gettacttgg cetttatece ettggettte etagaceetg gettgegeag etggatgeag 180 acaacatccc cccaccaccc aagagggagg gtagetette egecaccagg ggcaagcaca tttgtatcgg catttcacca acacgettat tttggcagtg gcagcatcca ttgtgtttat 300 349 atg aag ttc aga ata gtg aca tgt cag tcg gac tgg catctggaca acc Met Lys Phe Arg Ile Val Thr Cys Gln Ser Asp Trp 397 cgg gag ctg tgg gta gac gat gcc atc tgg cgc ttg ctg ttc tcc atg Arg Glu Leu Trp Val Asp Asp Ala Ile Trp Arg Leu Leu Phe Ser Met 15 20 445 atc ctc ttt gtc atc atg gtt ctc tgg cga cca tct gca aac aac cag Ile Leu Phe Val Ile Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln 30 493 agg ttt gcc ttt tca cca ttg tct gag gaa gag gag gat gaa caa Arg Phe Ala Phe Ser Pro Leu Ser Glu Glu Glu Glu Glu Asp Glu Gln 50 45 aag gag cct atg ctg aaa gaa agc ttt gaa gga atg aaa atg aga agt 541 Lys Glu Pro Met Leu Lys Glu Ser Phe Glu Gly Met Lys Met Arg Ser 65 589 acc aaa caa gaa ccc aat gga aat agt aaa gtt aac aaa gca cag gaa Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys Val Asn Lys Ala Gln Glu 80 85 gat gat ttg aag tgg gta gaa gag aat gtt cct tct tct gtg aca gat 637 Asp Asp Leu Lys Trp Val Glu Glu Asn Val Pro Ser Ser Val Thr Asp 100 gta gca ctt cca gcc ctt ctg gat tca gat gag gaa cga atg atc aca 685

Val Ala Leu Pro Ala Leu Leu Asp Ser Asp Glu Glu Arg Met Ile Thr

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Met	Lys	Thr	Leu	Phe	Leu	Asn	Thr	Glu	Tyr	Leu	Met	Pro	Phe	Leu	Leu	
1				5					10					15		
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														aca		333
Asn	Gin	GIA	-	Ser	Leu	Leu	ıyr	25	Leu	Thr	ьeu	AId	30	Thr	ASP	
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		35					40					45				
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	Ala	Gly	Met	Val		Thr	Val	He	Gly		Ser	Leu	Cys	Ile		
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		~++		+~~	201	~~~	<b>~</b> 33	ctc	a24	cta	cat	<b>a</b> a =	220	ggc	cac	525
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Ser	261	vai	FIO	85	1111	ALG	GIU	ДСи	90	Deu		017	<b>-</b> 275	95	0111	
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2+~	****		~~~~		<b>~</b> ~ ~ ~	*+ <i>~</i> ~	2200		- 2 (2 2	* +	~~~	~~~~	-~-	~+ = + <i>(</i>	raccea	747
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•	•				٠.				_	_	J J.	•	-	-		
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ttg gca tcg aca gat ctg acc ctg gct gtg ccc atc tgt aac tct ctg Leu Ala Ser Thr Asp Leu Thr Leu Ala Val Pro Ile Cys Asn Ser Leu 30 35 40	567
gct atc atc ttc aca ctg att gtt ggg aag gcc ctt gga gaa gat att Ala Ile Ile Phe Thr Leu Ile Val Gly Lys Ala Leu Gly Glu Asp Ile 45 50 55	615
ggt gga aaa cga gca gtt gct ggc atg gtg ctc acc gtg ata gga att Gly Gly Lys Arg Ala Val Ala Gly Met Val Leu Thr Val Ile Gly Ile 60 65 70 75	663
tca ctc tgc atc aca agc tca gtg agt aag acc cag ggg caa cag tct Ser Leu Cys Ile Thr Ser Ser Val Ser Lys Thr Gln Gly Gln Gln Ser 80 85 90	711
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170 175 180

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								ctg Leu								856
					_			acc Thr	-	-			-			904
						_	-	gca Ala			_		_			952
								gtc Val 255								1000
								Gly ggg							ggc '	1048
								gjå aaa								1096
								gtg Val								1144
ggc Gly	aac Asn	aag Lys	cag Gln	cac His 315	aac Asn	agt Ser	ccc Pro	acc Thr	tgg Trp 320	gat Asp	gac Asp	ccc Pro	acg Thr	ctg Leu 325	gcc Ala	1192
								gcc Ala 335								1240
ccc Pro	gag Glu	gtc Val 345	tcc Ser	cag Gln	gtg Val	acc Thr	aag Lys 350	tcc Ser	agc Ser	cca Pro	gag Glu	caa Gln 355	agc Ser	tac Tyr	cag Gln	1288
GJÀ aaa	gac Asp 360	atg Met	tac Tyr	ccc Pro	acc Thr	cgg Arg 365	ggc Gly	gtg Val	ggc	tat Tyr	gag Glu 370	acc Thr	atc Ile	ctg Leu	aaa Lys	1336
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aat Asn	Gly aaa	cag Gln	ctg Leu 410	ctg Leu	acc Thr	agt Ser	gtg Val	tac Tyr 415	cag Gln	ccc Pro	act Thr	gag Glu	atg Met 420	gcc Ala	ctg Leu	1480
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430

					gcc Ala			1576
					cag Gln 465			1624

435

1912

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475 480 tgagtcageg gtggcgagga gaggcggtcg gatttgggga gggccctgag gacctggccc 1732

egggeaaggg actetecagg etectectee ceetggeagg eccageaaca tgtgeeceag 1792

atgtggaagg geeteeetet etgeeagtgt ttgggtgggt gteatgggtg teeecaceca 1852

ggtcacactc cagccaaata gtgttctcgg ggtggtggct gggcagcgcc tatgtttctc 1972

ctcctcaqtg tttgtggagt cgaggagcca accccagcct cctgccagga tcacctcggc

tggagattcc tgcaacctca agagacttcc caggcgctca ggcctggatc ttgctcctct 2032

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acc cta tca ttg tta ttg aaa ttg tca cat tac tct tgt ctt tgg gtt 149 Thr Leu Ser Leu Leu Leu Lys Leu Ser His Tyr Ser Cys Leu Trp Val 25

aaa aaa gac ttt aaa gac tcc tcg ttt tac aat agc aat aat aat agc 197 Lys Lys Asp Phe Lys Asp Ser Ser Phe Tyr Asn Ser Asn Asn Asn Ser 40 45

aat agc aat cat tgt aaa tct tta ttg agc act cac tat atg cca ggc 245 Asn Ser Asn His Cys Lys Ser Leu Leu Ser Thr His Tyr Met Pro Gly 55

gct gta att agt aat tta tgc ctt atc tca tgt aaa gtt tcc agc agc 293 Ala Val Ile Ser Asn Leu Cys Leu Ile Ser Cys Lys Val Ser Ser Ser 70 75 80

cct att aag cag aca cat ggc att tcc atg tta cag atg aag aga ctg Pro Ile Lys Gln Thr His Gly Ile Ser Met Leu Gln Met Lys Arg Leu 90 95 100	341
aaa cac aca tta gct cgc ctt gcc cca ggg aca cat ggt ggg agc cag Lys His Thr Leu Ala Arg Leu Ala Pro Gly Thr His Gly Gly Ser Gln 105 110 115	389
aac tagg agttgageee aggeataetg atgeetggtg caettggaeg etgetgtaea Asn	446
gccactccag gtgtggatga gcaggaaaca cattgaag	484
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geggagetgt gtetgtteec aggagteett eggeggetgt tgtgteagtg geetgatege	180
g atg ggg aca aag gcg caa gtc gag agg aaa ctg ttg tgc ctc ttc Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe 1 5 10	226
ata ttg gcg atc ctg ttg tgc tcc ctg gca ttg ggc agt gtt aca gtg Ile Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val 20 25 30	274
Cac tot tot gaa cot gaa gto aga att cot gag aat aat cot gtg aag His Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys 35 40 45	322
ttg tcc tgt gcc tac tcg ggc ttt tct tct ccc cgt gtg gag tgg aag Leu Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys 50 55 60	<b>370</b>
ttt gac caa gga gac acc acc aga ctc gtt tgc tat aat aac aag atc Phe Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile 65 70 75	418
aca gct tcc tat gag gac cgg gtg acc ttc ttg cca act ggt atc acc Thr Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr 80 85 90 95	466
ttc aag tcc gtg aca cgg gaa gac act ggg aca tac act tgt atg gtc Phe Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val 100 105 110	514

115 120 125

115 120 125	
gtg ctt gtg cct cca tcc aag cct aca gtt aac atc ccc tcc tct gcc Val Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala 130 135 140	610
acc att ggg aac cgg gca gtg ctg aca tgc tca gaa caa gat ggt tcc Thr Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser 145 150 155	658
CCA CCT tCT gaa tac acc tgg ttc aaa gat ggg ata gtg atg cCT acg Pro Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr 160 165 170 175	706
aat ccc aaa agc acc cgt gcc ttc agc aac tct tcc tat gtc ctg aat Asn Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn 180 . 185 . 190	754
ccc aca aca gga gag ctg gtc ttt gat ccc ctg tca gcc tct gat act Pro Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr 195 200 205	802
gga gaa tac agc tgt gag gca cgg aat ggg tat ggg aca ccc atg act Gly Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr 210 215 220	850
tca aat gct gtg cgc atg gaa gct gtg gag cgg aat gtg ggg gtc atc Ser Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile 225 230 235	898
gtg gca gcc gtc ctt gta acc ctg att ctc ctg gga atc ttg gtt ttt Val Ala Ala Val Leu Val Thr Leu Ile Leu Gly Ile Leu Val Phe 240 245 250 255	946
ggc atc tgg ttt gcc tat agc cga ggc cac ttt gac aga aca aag aaa Gly Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys 260 265 270	994
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teacegeeta teatetgeat ttgeettaet eaggtgetae eggaetetgg eccetgatgt	1152
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tectaceact getgagtgge etggaacttg tttaaagtgt ttatteecca tttetttgag	1332
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48

teg gge ttt tet eet eet egt gea get tee tat gag gae egg gtg ace 144 Ser Gly Phe Ser Ser Pro Arg Ala Ala Ser Tyr Glu Asp Arg Val Thr

tte ttg cca act ggt atc acc tte aag tee gtg aca egg gaa gae act 192 Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val Thr Arg Glu Asp Thr 50

ggg aca tac act tgt atg gtc ttt gag gaa ggc ggc aac agc tat ggg 240 Gly Thr Tyr Thr Cys Met Val Phe Glu Glu Gly Gly Asn Ser Tyr Gly

gag gtc aag gtc aag ctc atc gtg ctt gtg cct cca tcc aag cct aca 288 Glu Val Lys Val Lys Leu Ile Val Leu Val Pro Pro Ser Lys Pro Thr 85

gtt aac atc ccc tcc tct gcc acc att ggg aac cgg gca gtg ctg aca 336 Val Asn Ile Pro Ser Ser Ala Thr Ile Gly Asn Arg Ala Val Leu Thr 105

tgc tca gaa caa gat ggt tcc cca cct tct gaa tac acc tgg ttc aaa

Cys	Ser	Glu 115	Gln	Asp	Gly	Ser	Pro 120	Pro	Ser	Glu	Tyr	Thr 125	Trp	Phe	Lys	
gat Asp	999 Gly 130	ata Ile	gtg Val	atg Met	cct Pro	acg Thr 135	aat Asn	ccc Pro	aaa Lys	agc Ser	acc Thr 140	cgt Arg	gcc Ala	ttc Phe	agc Ser	432
aac Asn 145	tct Ser	tcc Ser	tat Tyr	gtc Val	ctg Leu 150	aat Asn	ccc Pro	aca Thr	aca Thr	gga Gly 155	gag Glu	ctg Leu	gtc Val	ttt Phe	gat Asp 160	480
ccc Pro	ctg Leu	tca Ser	gcc Ala	tct Ser 165	gat Asp	act Thr	gga Gly	gaa Glu	tac Tyr 170	agc Ser	tgt Cys	gag Glu	gca Ala	cgg Arg 175	aat Asn	528
gjå aaa	tat Tyr	GJ Å 333	aca Thr 180	ccc Pro	atg Met	act Thr	tca Ser	aat Asn 185	gct Ala	gtg Val	cgc Arg	atg Met	gaa Glu 190	gct Ala	gtg Val	576
			gtg Val													624
			atc Ile													672
cac His 225	ttt Phe	gac Asp	aga Arg	aca Thr	aag Lys 230	aaa Lys	gj aaa	act Thr	tcg Ser	agt Ser 235	aag Lys	aag Lys	gtg Val	att Ile	tac Tyr 240	720
			agt Ser													768
	ctg Leu															777
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		1> C	:DS 515)	(1	.333)											·
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tggg	aaga	tg g	gact	gcag	a gg	ccag	ctgc	ctc	tatg	ctg	ccct	attc	ga c	ttcc	aatca	120
gcca	gctg	cc <sub>.</sub> t	ctac	actg	c cc	tatt	cgac	ttc	caat	cag	ccag	ctgc	gt c	taca	ctgcc	180
ctat	tcga	ct t	ccaa	tcag	с са	gctg	cctc	tac	actg	ccc	tatt	cgtc	tt c	caat	cagec	240

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tgcctctaca ctgccctatt cgacttccaa tcagccagct gcgtctacac cggaagccta	420
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attccttgtg gcctctgcgg gtcctgcctc agcc atg atg atc cac ggc ttc Met Met Ile His Gly Phe  1 5	532
cag age age cae egg gat the tge the ggg eee tgg aag etg acg geg Gln Ser Ser His Arg Asp Phe Cys Phe Gly Pro Trp Lys Leu Thr Ala 10 15 20	580
tcc aag acc cac atc atg aag tcg gcg gat gtg gag aaa tta gcc gat Ser Lys Thr His Ile Met Lys Ser Ala Asp Val Glu Lys Leu Ala Asp 25 30 35	628
gaa tta cat atg cca tct ctc cct gaa atg atg ttt gga gac aac gtt Glu Leu His Met Pro Ser Leu Pro Glu Met Met Phe Gly Asp Asn Val 40 45 50	676
tta aga atc cag cat ggg tct ggc ttt gga att gag ttc aat gct aca Leu Arg Ile Gln His Gly Ser Gly Phe Gly Ile Glu Phe Asn Ala Thr 55 60 65 70	724
gat gcg tta aga tgt gta aac aac tac caa gga atg ctt aaa gtg gcc Asp Ala Leu Arg Cys Val Asn Asn Tyr Gln Gly Met Leu Lys Val Ala 75 80 85	772
tgt gct gaa gag tgg caa gaa agc agg acg gag ggt gaa cac tcc aaa Cys Ala Glu Glu Trp Gln Glu Ser Arg Thr Glu Gly Glu His Ser Lys 90 95 100	820
gag gtt att aaa cca tat gat tgg acc tat aca aca gat tat aag gga Glu Val Ile Lys Pro Tyr Asp Trp Thr Tyr Thr Thr Asp Tyr Lys Gly 105 110 115	868
acc tta ctt gga gaa tct ctt aag tta aag gtt gta cct aca aca gat Thr Leu Leu Gly Glu Ser Leu Lys Leu Lys Val Val Pro Thr Thr Asp 120 125 130	916
cat ata gat aca gaa aaa ttg aaa gcc aga gaa cag att aag ttt ttt His Ile Asp Thr Glu Lys Leu Lys Ala Arg Glu Gln Ile Lys Phe Phe 135 140 145 150	964
gaa gaa gtt ctc ctt ttt gag gat gaa ctt cat gat cat gga gtt tca Glu Glu Val Leu Leu Phe Glu Asp Glu Leu His Asp His Gly Val Ser 155 160 165	1012
agc ctg agt gtg aag att aga gta atg cct tct agc ttt ttc ctg ctg Ser Leu Ser Val Lys Ile Arg Val Met Pro Ser Ser Phe Phe Leu Leu 170 175 180	1060
ttg cgg ttt ttc ttg aga att gat ggg gtg ctt atc aga atg aat gac Leu Arg Phe Phe Leu Arg Ile Asp Gly Val Leu Ile Arg Met Asn Asp 185 190 195	1108
acg aga ctt tac cat gag gct gac aag acc tac atg tta cga gaa tat Thr Arg Leu Tyr His Glu Ala Asp Lys Thr Tyr Met Leu Arg Glu Tyr 200 205 210	1156
acg tca cga gaa agc aaa att tct agt ttg atg cat gtt cca cct tcc Thr Ser Arg Glu Ser Lys Ile Ser Ser Leu Met His Val Pro Pro Ser 215 220 225 230	1204

Ctc ttc acg gaa cct aat gaa ata tcc cag tat tta cca ata aag gaa Leu Phe Thr Glu Pro Asn Glu Ile Ser Gln Tyr Leu Pro Ile Lys Glu 235 240 245	1252
gca gtt tgt gag aag cta ata ttt cca gaa aga att gat cct aac cca Ala Val Cys Glu Lys Leu Ile Phe Pro Glu Arg Ile Asp Pro Asn Pro 250 255 260	1300
gca gac tca caa aaa agt aca caa gtg gaa taa aatgtgat acaacatata Ala Asp Ser Gln Lys Ser Thr Gln Val Glu * 265 270	1351
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	atg Met															644
	tgc Cys 100															692
	GJA aaa															740
	atg Met															788
	tgc Cys	_					-						_	_		836
	gaa Glu		Val		_				_	_	_				-	884
	atg Met 180				-	-	-		-		_		_			932
	tcc Ser	_		-						-	Ile		-			980
	gtt Val				Leu								_		-	1028
	ggt Gly			Tyr							aaaa	agag	c tt	tgtt	tggt	1079
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act tot tgc ctg gct toa ggg cot gta cac atg gga act tot tgc of the Ser Cys Leu Ala Ser Gly Pro Val His Met Gly Thr Ser Cys 100 105 110	
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554

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Lys Phe Asn Leu Lys Leu Val Ile Lys Pro Ala Lys Val Thr Pro Ala

125 130 135

125 130 135	
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acc agg gga cat ggc cca gca gag aca cag aca ctg ggg agc ctc cct Thr Arg Gly His Gly Pro Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro 155 160 165	650
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age act tet gag gag cag gge tgg gte cet gee ace tac etg gag gee

Ser Thr Ser Glu Glu Gln Gly Trp Val Pro Ala Thr Tyr Leu Glu Ala

45

50

556

Cag aat ggt act egg gat gae tee gae ate aae ace tet aag act gga
Gln Asn Gly Thr Arg Asp Asp Ser Asp Ile Asn Thr Ser Lys Thr Gly

60

65

70

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Trp Thr Leu Gly Gly Met Val Asn Arg Gln His Ser Arg Glu Glu Lys

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	-												_	tgc Cys		1996
								_				_		gac Asp	_	2044
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	-	_		_	_			-					_	gca Ala 600		2188
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_						-				_			-	agt Ser		2284
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1 5 10

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Phe Leu Thr Phe Gly Ser Ile Leu Ala Leu Leu Ala Gly Lys Ala Cys

15 20 25

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PCT/US01/02623 WO 01/55437 ctt tac tee tta eee ttt tat ett tte ttt aaa ett teg eet eta aat Leu Tyr Ser Leu Pro Phe Tyr Leu Phe Phe Lys Leu Ser Pro Leu Asn 55 45 ctg cca ggg aaa ttg gga ctt ata gaa acc ttg tca act tgt ttg ggt 421 Leu Pro Gly Lys Leu Gly Leu Ile Glu Thr Leu Ser Thr Cys Leu Gly 70 65 469 caa aaa tta gat cct gtg tta gaa act ctg caa aga gtg aga tcc atg Gln Lys Leu Asp Pro Val Leu Glu Thr Leu Gln Arg Val Arg Ser Met 80 gca tca ttg atc gcc aac ttc ttt gtt cct ttc atc cag aag aaa ggt 517 Ala Ser Leu Ile Ala Asn Phe Phe Val Pro Phe Ile Gln Lys Lys Gly 105 cag etc att acg taa gaaactttte atcaggaaaa geagacaace gataaaaaac 572 Gln Leu Ile Thr \* 110 632 agaaactaag tattctgcaa ggaaacctgg tttaaggaga atgtattgaa actggatatg cetgtteett tttacteete cetttggeat tteettttt tttetgtaag ataateatag 692 aaatttaggt aatggcggga ctacaaagat cacatggctt tatgggcccg cctattatgc 752 754 .tg <210> 47 <211> 859 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (23)..(715) <400> 47 cagcategga ggtegeteag ee atg gea tgg ate eet ete tte ete gge gte 52 Met Ala Trp Ile Pro Leu Phe Leu Gly Val ctt gct tac tgc aca gga tcc gtg gcc tcc tat gag ctg act cag cca 100 Leu Ala Tyr Cys Thr Gly Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro cec tea gtg tee gtg tee eea gge aag aca gee age ate ace tge tet 148 Pro Ser Val Ser Val Ser Pro Gly Lys Thr Ala Ser Ile Thr Cys Ser 30 196 gga gat aaa ttg ggg gat aaa tat gct tcc tgg tat cag cag aag gca Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Ala 45 ggc cag tcc ccc gtg ctg gtc atc tat cga cat agc aag cgg ccc tca 244 Gly Gln Ser Pro Val Leu Val Ile Tyr Arg His Ser Lys Arg Pro Ser 60 65 ggg atc cct gag cga ttc tct ggc tcc aat tct ggg aac aca gcc act 292 Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr

80

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	Ser					His					Суз				gaa Glu 260		822
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		tcc Ser 30															385
		tta Leu															433
		gcc Ala		_						-						•	481
		tcc Ser															529
		aat Asn															577
		aaa Lys 110															625
		agt Ser															673
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tta Leu	att Ile	ttt Phe	att Ile	ttt Phe 160	caa Gln	gtg Val	ttt Phe	aaa Lys	aaa Lys 165	ttc Phe	aat Asn	ttt Phe	aat Asn	tta Leu 170	ttt Phe		769
agg Arg	cat His	ttg Leu	tta Leu 175	gta Val	aca Thr	gat Asp	tct Ser	tac Tyr 180	tct Ser	cat His	atc Ile	taag	j aag	jttt	tca 5	*	819
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1001

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gcg gct cac atc atg gca gca agc ctc atc aga Ala Ala His Ile Met Ala Ala Ser Leu Ile Se 85 90	c aag cca gtg aga ggg 34: r Lys Pro Val Arg Gly 95
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458

518

539

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                                                 20
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                                                                      472
Gln Ser His Gly Ser Thr Arg Leu Gln Ser Thr Ile Thr Thr His Trp
aga atg ggg gcg aca tgg tcc acc tga aagat cttaacaccc aggctgtgag
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cgc Arg	cga Arg	aaa Lys	cgg Arg 20	cga Arg	acg Thr	aca Thr	aac Asn	999 Gly 25	gag Glu	ggc Gly	cgg Arg	aat Asn	gcg Ala 30	gca Ala	agg Arg	96
cac His	gcc Ala	35 Gly ggg	aaa Lys	gag Glu	gga Gly	aac Asn	ccg Pro 40	cga Arg	aag Lys	ccc Pro	acg Thr	ggc Gly 45	aac Asn	gcc Ala	caa Gln	144
acc Thr	ccc Pro 50	atg Met	gac Asp	cca Pro	agg Arg	aaa Lys 55	cgt Arg	aaa Lys	aag Lys	gga Gly	agt Ser 60	ctg Leu	acc Thr	ccg Pro	gga Gly	192
cca Pro 65	aat Asn	aga Arg	cgc Arg	caa Gln	cag Gln 70	gaa Glu	agc Ser	gag Glu	ggc Gly	gca Ala 75	agg Arg	aga Arg	caa Gln	tcg Ser	cga Arg 80	240
cgg Arg	gga Gly	gag Glu	aac Asn	999 Gly 85	agc Ser	gaa Glu	gca Ala	gcc Ala	cag Gln 90	agc Ser	ccc Pro	agc Ser	cgg Arg	gga Gly 95	acg Thr	288
gaa Glu	cgg Arg	aag Lys	gca Ala 100	acc Thr	aag Lys	agg Arg	gtg Val	aaa Lys 105	aga Arg	aag Lys	caa Gln	gac Asp	gtc Val 110	acc Thr	glà aaa	336
aat Asn	gac Asp	cca Pro 115	cat His	agc Ser	cct Pro	tct Ser	ttg Leu 120	tct Ser	tcg Ser	gga Gly	ggt Gly	ccc Pro 125	atc Ile	cat His	aaa Lys	384
gcc Ala	aac Asn 130	Thr	tcc Ser	gga Gly	aga Arg	tta Leu 135	aag Lys	gtg Val	tcg Ser	gac Asp	agg Arg 140	Gly 999	aca Thr	gct Ala	gag Glu	432
agg Arg 145	Arg	gga Gly	gga Gly	ttt Phe	ctt Leu 150	gcc Ala	agg Arg	tgg Trp	aga Arg	gtc Val 155	Phe	acc Thr	gtc Val	tgt Cys	tgg Trp 160	480
gtg Val	cag Gln	gcc Ala	tgt Cys	gtc Val 165	Cys	cct Pro	gga Gly	aag Lys	atg Met 170	Leu	gca Ala	atg Met	gly aaa	gcg Ala 175	ctg Leu	528
gca Ala	gga Gly	ttc Phe	tgg Trp 180	Ile	ctc Leu	tgc Cys	ctc Leu	ctc Leu 185	Thr	tat Tyr	ggt Gly	tac Tyr	ctg Leu 190	Ser	tgg Trp	576
ggc	cag Gln	gcc Ala 195	Leu	gaa Glu	gag Glu	gag Glu	gaa Glu 200	ı Glu	ggg Gly	gcc Ala	tta Leu	cta Leu 205	Ala	caa Gln	gct Ala	624
gga Gly	gag Glu 210	Lys	cta Leu	gag Glu	cec Pro	ago Ser 215	Thr	act Thr	tcc Ser	acc Thr	Ser 220	Gln	ccc Pro	cat His	ctc Leu	672
att Ile 225	Phe	ato Ile	cta Leu	gcg Ala	gat Asp 230	Asp	cag Glr	gga Gly	ttt Phe	aga Arg 235	Asp	gtg Val	ggt Gly	tac Tyr	cac His 240	720
gga Gl	tct Ser	gag Glu	att Ile	aaa Lys	aca Thr	cct Pro	act Thr	ctt Leu	gac Asp	aag Lys	cto Leu	gct Ala	gcc Ala	gaa Glu	gga Gly	768

	245	250	255
gtt aaa ctg gag Val Lys Leu Glu 260	Asn Tyr Tyr Val (	cag cct att tgc aca Gln Pro Ile Cys Thr 265	cca tcc agg 816 Pro Ser Arg 270
agt cag ttt att Ser Gln Phe Ile 275	act gga aag tat o Thr Gly Lys Tyr o 280	cag ata cac acc gga Gln Ile His Thr Gly 289	Leu Gln His
tct atc ata aga Ser Ile Ile Arg 290	cct acc caa ccc a Pro Thr Gln Pro 2 295	aac tgt tta cct ctg Asn Cys Leu Pro Leu 300	g gac aat gcc 912 1 Asp Asn Ala
acc cta cct cag Thr Leu Pro Gln 305	aaa ctg aag gag Lys Leu Lys Glu 310	gtt gga tat tca acg Val Gly Tyr Ser Thi 315	g cat atg gtc 960 c His Met Val 320
gga aaa tgg cac Gly Lys Trp His	ttg ggt ttt tac Leu Gly Phe Tyr 325	aga aaa gaa tgc atg Arg Lys Glu Cys Mei 330	g ccc acc aga 1008 E Pro Thr Arg 335
aga gga ttt gat Arg Gly Phe Asp 340	Thr Phe Phe Gly	tcc ctt ttg gga ag Ser Leu Leu Gly Se 345	t ggg gat tac 1056 r Gly Asp Tyr 350
tat aca cac tac Tyr Thr His Tyr 355	aaa tgg gac agt Lys Trp Asp Ser 360	ccc tgg gat gtg tg Pro Trp Asp Val Tr 36	o Leu
tatganaacg acca	tgctgc ctgggactat	gacaatggca tatact	tcac acagatgtac 1165
actcagagag gaca	agccaat cctagctttc	cataacccca caaggc	ctaa aattttaaaa 1225
atggccatcc aago	egggtca tttcccactg	ggaggteeet gggagg	gatt tcgaacactt 1285
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gaagggacta tggctggtct ttgtactttt ttttccaact tttctgtagg tttaaaattt 180
tcaaaataaa aaatgggaaa tactttaaaa attgtaatca aagacattag tacagaaact 240
ttcataatgt attttattt tacagtaaaa ttaatttatg taaattgata gaattttact 300
aatttcactc ccaagttaca ttaaaaggct tacatatgtt tgataatagc atatgtaaac 360
tagaactctg aatgatatcc attggtcata atacgtacta tgtagcggta atggtgactt 420

•	
ttgtgattgc acaagtctag agatgcccca aatgacattg acttagacat ctggttattc	480
taaggotgaa actgaagttg aatagaaggt tttagtcaaa tactgagatg aaaactgagg	540
cagtcctggc ggggggggt gagtgtgtgt gtatatatac acacatagac atcatgcttc	600
taaacattta cagaaagaaa gggtagatta tctacaaaaa aataagaatc agactgatat	660
gagatettae aaacetaace ceettetett teetaaacte cagattetea tatttetgae	720
ttcctatttg atatttacac ttcgatattt accaggagtc ttcaacattt tgttcaaaac	780
agtactettg gttttettee tecaagacta eteettaete atateageaa atageagete	840
ttttcaagtg ctcagtgtaa aaacctacaa ttaatccttg atttctcttt cagtcagcct	900
atactaaatc aatttcattt aaaatatctc ggctactact ctgcatctcc actgctacca	960
toggeotete cagteacatt etceaagage actetatete atttaaaaga caaaatetet	1020
gcagtggcct gtgatgctcc tta atg gcc tac ata atc cag ccc tca agc Met Ala Tyr Ile Ile Gln Pro Ser Ser 1 5	1070
acc tcc gtg atc tct gta aaa ctt tcc ctt ggt cac tgt gct tca gcc Thr Ser Val Ile Ser Val Lys Leu Ser Leu Gly His Cys Ala Ser Ala 10 15 20 25	1118
aca tta acc agc ttg cat att tct cac att cac caa gct tgt tcc tgc Thr Leu Thr Ser Leu His Ile Ser His Ile His Gln Ala Cys Ser Cys 30 35 40	1166
ctt ggg gcc ttt gta ctt acc atg ttc tgt tct gag aat act ctg cct Leu Gly Ala Phe Val Leu Thr Met Phe Cys Ser Glu Asn Thr Leu Pro 45 50 55	1214
caa gat atc cta caa cta tct tac tgt att cag ctc tct gct caa gta Gln Asp Ile Leu Gln Leu Ser Tyr Cys Ile Gln Leu Ser Ala Gln Val 60 65 70	1262
tta act gat gaa acc tgt cat ccc tac tcc act cca tgt tct gct tta Leu Thr Asp Glu Thr Cys His Pro Tyr Ser Thr Pro Cys Ser Ala Leu 75 80 85	1310
ctt aac agc aat tgc aca tat ggc ccc ctg aat aat ata cat tta gtc Leu Asn Ser Asn Cys Thr Tyr Gly Pro Leu Asn Asn Ile His Leu Val 90 95 100 105	1358
act tat ttt tac tta tct gct aat taaaatgtag actttttcta ttctgtttac Thr Tyr Phe Tyr Leu Ser Ala Asn 110	1412
tgctgtattc ccagcatgtt ttatccgaat gtgcagtggt ttcttttctt	1472
gtgggaagtg atgtgcacaa atacacataa tggagcctga atgtcatatt gctttcatac	1532
ctgtgtgaat tttggtaaga aaggaaaagt agcgattgac aggtaatata attacattaa	1592
gtcactctca tagttagctg tttattgctt tcctgctctt attctcagtc cccaggacca	1652
aatgttgacc actaccttcc cccacatata attaggttat ttaccgaacg ccatgcaggt	1712
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1786

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tgacttctaa cattctgtaa aataatttga gagtactagt taactaattc acaaacttta	180
aattagtagt ttattttcag ttaagcacac aagaaagaaa tatacagtct atctataatg	240
aaatcttagt tgactagatg ggttgtggtg tcttaaaaat tcccataact gatcacatgg	300
ettttaaaat aggaagtetg agatttttt gtttteetea actatateet ttttaacaag	360
ttctatttt atg gat ctt tat gta gtg att ttt tgg tta gta tac ata Met Asp Leu Tyr Val Val Ile Phe Trp Leu Val Tyr Ile 1 5 10	408
ttc tct act tac ata atc aca tat ata aaa ggt aat gtg gga ctg tgt Phe Ser Thr Tyr Ile Ile Thr Tyr Ile Lys Gly Asn Val Gly Leu Cys 15 20 25	456
ttt caa atc tta ttt cag cta agt ttt gag aga aga cca aaa tca gta Phe Gln Ile Leu Phe Gln Leu Ser Phe Glu Arg Arg Pro Lys Ser Val 30 35 40 45	504
agg taa gctgagaact aagagtagaa agtttaaact agagcagggg ccaagtttag Arg *	560
gagcagccac aacttttctt gcacatcaac ttagttgtaa caatttagtt tgaaagaaaa	620
totggaacat aatactcagt ttgtaaaatt gaagttggta gaatt	665
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ccccatcagt gctctgagta ggctgtcatc agaacaaagg gctccactgc tgacaaggtt	180
tgagaactgc tggcttgagg tgagaacccc tttaacctct gcgggacagc atg tct Met Ser 1	236
ttc cct atc cac ctt cga ttc ttt tct ctt ttt ttt ctt cat tgg ctc Phe Pro Ile His Leu Arg Phe Phe Ser Leu Phe Phe Leu His Trp Leu 5 10 15	284
ctt ctt agt gga ttc tct tct cta ctg ccc tgg gct tca gcc ttt gtg Leu Leu Ser Gly Phe Ser Ser Leu Leu Pro Trp Ala Ser Ala Phe Val 20 25 30	332
cag tac tct cga tgc cct gaa cac aca cct tcc ctt tgc cca ggc ggt Gln Tyr Ser Arg Cys Pro Glu His Thr Pro Ser Leu Cys Pro Gly Gly 35 40 45 50	380
gca aac aat cca ctt ctt caa gct cca aca caa atg ctg cct cct tta Ala Asn Asn Pro Leu Leu Gln Ala Pro Thr Gln Met Leu Pro Pro Leu 55 60 65	428
gga tgc ctg ctc tgt gct ctc cct gcc tcc cct agc cca tac ctc tgc Gly Cys Leu Leu Cys Ala Leu Pro Ala Ser Pro Ser Pro Tyr Leu Cys 70 75 80	476
tgg cac ctt ctg tac cat gcc ttc aga aac ctt ctt atc ccc ctc atc Trp His Leu Leu Tyr His Ala Phe Arg Asn Leu Leu Ile Pro Leu Ile 85 90 95	524
Ser Gly Ala Pro Cys Gly Ser Gly Ile Pro Lys Phe Ser Lys Cys Leu 100 105 110	572
tca gta agc tgatggt acatgcattt tctaaaatag agctgggact tcccatgggg Ser Val Ser 115	628
cccacatetg acctggcage ccatgtatte eggecattag ggatgggaag ccatgaggae	688
ctggccttct gcccgaccca ggcagccatt caaggtgagc aatggccact tccaagactc	748
aagtgcacct ggaccctgcc caacaggccc ccccaggaaa aacaggctgt ccctggcggc	808
agtaagtagc aggcggccca aggtttctgg agctcttggt tttggcccaa ccccccacc	868
caaaatactg ggttaggaca ggggacttgt agctccccct cagtgacctt tggccctggg	928
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<213> Homo sapiens

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tcctttgtct tagtagatgg gtccttcttt tattataact agagttttaa gttttctttt 180
attagggcat ttgaataaaa aacaatcatt gtagaagtat aattaattaa taactagtaa 240
tcttatgtca tcttgaggga atc atg ctg gga tgg caa atc tgg aga ctg 290
Met Leu Gly Trp Gln Ile Trp Arg Leu

1 5

agg Arg 10	cca Pro	caa Gln	ctc Leu	ctc Leu	tcc Ser 15	ttc Phe	cat His	aca Thr	cag Gln	gac Asp 20	aga Arg	tgt Cys	cac His	tgg Trp	tct Ser 25	3	38
			caa Gln													3	86
			cta Leu 45													4	34
ctat	tcaa	ac a	attt	ctta	a ag	raata	tgca	atg	cata	ata	aggg	gttg	gag a	ataca	gaatg	4	94
ctac	ttta	ict a	aaat	acta	ıc ag	rtgta	agaa	tgt	atag	jaaa	aaag	caca	itg o	tttg	gagac	5	54
ttaa	aggo	ct ç	ggta	ıtgaa	ıt ca	tggc	tctg	aca	ttaa	ıcaa	acct	cacc	tc o	tett	taaaa	6:	14
gagt	aata	at ç	gattg	gtat	c to	attg	agct	ccg	rtaaa	icta	aaaa	ctac	ag a	ıgtaa	gaagg	6	74
gggg	gccc	tt a	ıcaaa	agct	t tg	gagg	ggga	caa	acct	gcg	gctg	agto	at g	gcto	tgact	· 7:	34
ttat	ctcc	ca t	cacc	gcct	c to	taaa	agat	aaa	aagg	att	gttt	ggca	tg ç	agct	tttta	79	94
ttag	gaaa	iga a	ι				•									80	05

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WO 01/55437	PCT/US01/02623
50 55	60
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attgttttct ctgtaacttt actatcatct acctatcttc gtattttg	gt gagagatcat 422
gaaaccctct atcaaactct ctttatgcag taagttataa caaattagc	ca ctggcttata 482
aagatatatc aaattagagt aaaatgcaac tgaaaatatc ataaatca	tt cggtaattaa 542
tgttttctta aattcttggg gnaagtacaa gagaagaaat tggagatg	tg cagactttaa 602
atgacctaaa cagtcttaca caggagtttt tgcagtatgg taagaagga	ag gtggctactt 662
atgttttcaa aaagcacatg acctcatgaa aagtatgcaa ggctatac	tg tegaeggtag 722
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aaaagctata cacagaaaag ctgcttaatt tataacattt tttgaaagc	ca ggtcactgaa 180
ttactactga cagecaegtg aatttetgee agggtaagtg gaaaaaagt	ng accaaaaggg 240
agaaccaa atg agt gtg cag gca tcc agg gga gcg ggt cag Met Ser Val Gln Ala Ser Arg Gly Ala Gly Gln 1 5 10	cac agc aca 290 His Ser Thr
cta gat gaa aaa ggc tcg gaa aga tct ctg tcg tgt gca g Leu Asp Glu Lys Gly Ser Glu Arg Ser Leu Ser Cys Ala I 15 20 25	Jac ggt ttc 338 Asp Gly Phe 30
cat gtc tgt tta aat gac aac acg aac agc aga aaa ata g His Val Cys Leu Asn Asp Asn Thr Asn Ser Arg Lys Ile 0	gag aaa acc 386 Glu Lys Thr 45

agt aaa toa gtt got toa tot coa toa tac ogo gag gto tgactacott Ser Lys Ser Val Ala Ser Ser Pro Ser Tyr Arg Glu Val

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tettttttg ggtgtggtgg ggtatette

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                                                                       53
                             Met Ser Tyr Ser Thr Pro Ala Trp His
gag gga tgt agg tac gag aat aca gaa tac ggg tgt ttt cta tta agc
                                                                      101
Glu Gly Cys Arg Tyr Glu Asn Thr Glu Tyr Gly Cys Phe Leu Leu Ser
                     15
aca cac att aca gag att tgc aaa aat gtt aca atg ctg ctc ttc tca
Thr His Ile Thr Glu Ile Cys Lys Asn Val Thr Met Leu Leu Phe Ser
                                     35
cta aac ttt ttc ttt tgg aaa ata gtc atg ttt cat aaa aat gta ata
                                                                      197
Leu Asn Phe Phe Phe Trp Lys Ile Val Met Phe His Lys Asn Val Ile
                                 50
ttt ata tta aca tgt aat ggg ttt att att gtt act ttt aaa tgg att
                                                                      245
Phe Ile Leu Thr Cys Asn Gly Phe Ile Ile Val Thr Phe Lys Trp Ile
         60
gat aaa ttt att tta aat att tct att tta att tct aac aca gta aat
                                                                      293
Asp Lys Phe Ile Leu Asn Ile Ser Ile Leu Ile Ser Asn Thr Val Asn
     75
gtt aat agc cat aat cca cat aaa caa aag ttc ttt ggg gat ctc agt
Val Asn Ser His Asn Pro His Lys Gln Lys Phe Phe Gly Asp Leu Ser
aat ttt taacagogta aaggggtoot gagaccaaaa agtttgagaa otgotgcaat
                                                                      397
Asn Phe
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tgatcaataa gggcttaaat atg
                                                                     480
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gcg cat aag aat gtc ctg gca gca ttc agc cag tat ttt agg aat gtt Ala His Lys Asn Val Leu Ala Ala Phe Ser Gln Tyr Phe Arg Asn Val 15 20 25	159											
cag cag atg cac agc aga aca aaa cgt tgg atg aat cgc atc cgc atg Gln Gln Met His Ser Arg Thr Lys Arg Trp Met Asn Arg Ile Arg Met 30 35 40	207											
ctt cac cat cag tta atc gtc atc act ccg cag gtg aaa tct caa aac Leu His His Gln Leu Ile Val Ile Thr Pro Gln Val Lys Ser Gln Asn · 45 50 55	255											
aag ctc ctg ata ctt cag atg gca gct gca cag aac tgc ctt tca aac Lys Leu Leu Ile Leu Gln Met Ala Ala Ala Gln Asn Cys Leu Ser Asn 60 65 70	303											
agc caa att act att aca aac tca gaa act ttt aca cct gtg aat gac Ser Gln Ile Thr Ile Thr Asn Ser Glu Thr Phe Thr Pro Val Asn Asp 75 80 85 90	351											
tct gcc cca cac cct gag tca gac gcc aca tgc caa caa cct gtc aag Ser Ala Pro His Pro Glu Ser Asp Ala Thr Cys Gln Gln Pro Val Lys 95 100 105	399											
cag atg agg ctc aaa aag gcc att cat ctg aag aag ctc aat ttc ctg Gln Met Arg Leu Lys Lys Ala Ile His Leu Lys Lys Leu Asn Phe Leu 110 120	447											
aag toa cag aaa tac goa gag caa gta tot gaa ooc aag toa gat gat Lys Ser Gln Lys Tyr Ala Glu Gln Val Ser Glu Pro Lys Ser Asp Asp 125 130 135	495											
ggt ttg aca aag agg ttg gaa tct gct agt aaa aat acc cta gag aaa Gly Leu Thr Lys Arg Leu Glu Ser Ala Ser Lýs Asn Thr Leu Glu Lys 140 145 150	543											
gct agc agc caa agt gct gaa gaa aaa gaa agt gaa gaa gtc gtc agt Ala Ser Ser Gln Ser Ala Glu Glu Lys Glu Ser Glu Glu Val Val Ser 155 160 165 170	591											
tgt gag aat ttt aat tgc att agt gag acg gag agg cct gaa gac ccg Cys Glu Asn Phe Asn Cys Ile Ser Glu Thr Glu Arg Pro Glu Asp Pro 175 180 185	639											
gct gcc ctg gaa gac cag tcc cag aca ctt cag tcc cag aga caa tac Ala Ala Leu Glu Asp Gln Ser Gln Thr Leu Gln Ser Gln Arg Gln Tyr 190 195 200	687											
gcg tgt gaa tta tgc ggg aaa cct ttt aaa cac cca agc aac ttg gag Ala Cys Glu Leu Cys Gly Lys Pro Phe Lys His Pro Ser Asn Leu Glu 205 210 215	735											
ctt cac aaa cgg tct cat aca ggt aac tga t tcagtaccca caggcagaag Leu His Lys Arg Ser His Thr Gly Asn * 220 225	786											

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145					150					155					160	
								_		gtc Val						707
_			_	_			_			gag Glu		_				755
		-	•		_	-				gag Glu		_	_	-		803
_	-		_	_		_			_	tcc Ser		_	_			851
_	_	_					_			aag Lys 235		-	_	_	_	899
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acg Thr	ccg Pro 370	acg Thr	aaa Lys	cac His	gct Ala	atc Ile 375	gtg Val	cag Gln	acc Thr	ctg Leu	gtg Val 380	cat His	ctc Leu	aag Lys	ttc Phe	1331
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atc Ile	tcc Ser	gtc Val	ctc Leu	tac Tyr	aag Lys	gat Asp	gac Asp	atg Met	gly aaa	gtg Val	ccc Pro	acc Thr	ctc Leu	aag Lys	tac Tyr	1427

405 410 415

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gag atc aaa gcc cca aga ata agg ctc atg tgg tcc cta ccc ttg agg Glu Ile Lys Ala Pro Arg Ile Arg Leu Met Trp Ser Leu Pro Leu Arg 30 35 40	147
aga caa aaa tat acg atg tag at ggacagetge attatgeaca cagateeatt Arg Gln Lys Tyr Thr Met  * 45	200
tcaatataac atggtgggct actetgggaa cacteetget ecacaaggag cagtataaaa	260
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<220>

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622

682

684

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cccatt atg cct gtt act cct gat cct tct gca gtc tct ctc ttt gtg Met Pro Val Thr Pro Asp Pro Ser Ala Val Ser Leu Phe Val 1 5 10	22
acc cca tgg cct ttg ctg cta tgt ctg ccc tgg ccc cac aga gtg cca Thr Pro Trp Pro Leu Leu Cys Leu Pro Trp Pro His Arg Val Pro 15 20 25 30	276
ggt cag agc cac cct ggc cta cat agc agg gcc ccg gtt cac agg cta Gly Gln Ser His Pro Gly Leu His Ser Arg Ala Pro Val His Arg Leu 35 40 45	324
aaa cct ggg cct cct gcc agg ctg caa ctc cca gct gca cac cgc aac Lys Pro Gly Pro Pro Ala Arg Leu Gln Leu Pro Ala Ala His Arg Asn 50 55 60	372
ctg aga cat ctc agc ata ttc tag gaactagtaa tggggacgct tccgactcgc Leu Arg His Leu Ser Ile Phe * 65 70	426
tggggaaggg agatgagggc ctctagctct ccatgcccag tctctcatca tcaaagtcat	486
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cat tgg tat tgt agc cct gat gac atg cag atg gtt gat ttc agc tca His Trp Tyr Cys Ser Pro Asp Asp Met Gln Met Val Asp Phe Ser Ser 25 30 35	150
aca tac gaa agg att ttc agg cca ttt gtg ttc aag ata aaa ggg cct Thr Tyr Glu Arg Ile Phe Arg Pro Phe Val Phe Lys Ile Lys Gly Pro 45 50 55	198
gac agc ttt agg ata gac atg agc ccc atc cct gaa gac att taa tca Asp Ser Phe Arg Ile Asp Met Ser Pro Ile Pro Glu Asp Ile * 60 65 70	246
caatctagac aagctcttgt tgtaaatgag ctcaagtatc agatttggaa gtgaatgatc	306

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gtg gtg cag tac cac tga ggactg ttgctgtatt gattaggaaa agagacagag Val Val Gln Tyr His * 145 150	603
taatttgcag tttgtttgat ttatactttt gtttatctac aacccaataa cagacatgag	663
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atc cgc cac tac gtg tcc atc ctg ctg cag agc gac aag aag ctc acc  Ile Arg His Tyr Val Ser Ile Leu Leu Gln Ser Asp Lys Lys Leu Thr  30 35 40 45	385
cag gaa caa gta tct gac agt caa gtc cta att cga agc aga gtc ctc Gln Glu Gln Val Ser Asp Ser Gln Val Leu Ile Arg Ser Arg Val Leu 50 55 60	433
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aag gta gtg cca cct tct cct atg act gat cct act atg ttg aca gac Lys Val Val Pro Pro Ser Pro Met Thr Asp Pro Thr Met Leu Thr Asp	577

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105

100

w	01/5	5437												]	PCT/U	S01/02623
Met 110	Met	Lys	Gly	Asn	Val 115	Thr	Asn	Val	Leu	Pro	Met	Ile	Leu	Ile	Gly 125	
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		_			-		_	cct Pro 150	_		_					721
				_	_			gtg Val	•		_					769
								att Ile								817
								atg Met								865
-	-	_	_	_		_	_	aca Thr			-		-			913
	_	-	-		_	_	-	cac His 230	-		-			_	-	961
								cct Pro								1009
				_				ttg Leu	_			_			-	1057
					agt Ser 275	_		taa *	ccti	g ta	aactt	tgtl	tgg	gaget	ggc	1109
acctcttgaa ataaaaagga ggatgcacga gctgggaaaa aaaaaa 11											1155					
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															ıcata	

ttatcttatt taagcctcgt agaaatctta tgagcaaaat gttactcggt acacttaaag

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tgetegtaae caetatattg taattteaaa eeetgattee	atta atg ctt ttt gtt 29 Met Leu Phe Val 1
gtg ttg cct tta ctg ata att gtg ttc aat att Val Leu Pro Leu Leu Ile Ile Val Phe Asn Ile 5 10	Pro Met Arg Glu Ala
gtc ttt gac ttt tta ttt atg ata aag att att Val Phe Asp Phe Leu Phe Met Ile Lys Ile Ile 25 30	aaa gtg ctt aaa gtt 39 Lys Val Leu Lys Val 35
ttt tat tgt ata gcg tgt ttt atc atc aag cag Phe Tyr Cys Ile Ala Cys Phe Ile Ile Lys Gln 40 45	gtt tta gtt ttt taa 44 Val Leu Val Phe * 50
ggtaaactga tcaaaaataa taaaaggtga tgggtttatg	acacttgggt ttgagagaac 50
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cagagatgcc ccaagaacac ttctaggttt attggttcga	aagaaaggac taccgggagt 62
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tctaagaacg actcattaaa ttacgtataa ttctttacta	cataaatgaa gttccctctt 24(
attoctattt tactttttt ttaaattagg a atg gtt Met Val 1	act tat ttt atc aaa 292 Thr Tyr Phe Ile Lys 5
tgc ttt cat tat gag gtt tct ttt ctt ctt tgg Cys Phe His Tyr Glu Val Ser Phe Leu Leu Trp 10	Phe Ala Val Val Arg 20
aat gat gta gac agg cca gtc tcc ctg tca ctc Asn Asp Val Asp Arg Pro Val Ser Leu Ser Leu 25	Phe Ser Ser Tyr Ser 35
tta ttc tca aca tat cca gac aca tgt ccc ttg	ttc aaa ctc ccc acc 436

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Leu Phe Ser Thr Tyr Pro Asp Thr Cys Pro Leu Phe Lys Leu Pro Thr 40 45 50 55	
cac tta ctg tgt tgt tta gag gaa ata taa a tgtccttatt ataactgaca His Leu Leu Cys Cys Leu Glu Glu Ile * 60 65	487
aggccctacc ctgttcaatc ttactacttt tctgcctaat ctacttctct ctctctatct	547
aactcatcct actcagtcat cttggctttc ttgatgttcc tggaatatac tggacatgtt	607
ccctttacag agccttttca gttgctcgtc tccttacctt ggatgtattt ccatcccaca	667
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ttctaagatt gttttcttaa aattagaaga ctgatgttgt attattaaaa acaaccaact	240
caccatgctt cagggtagag attcttttgt ctattgcta atg gag gat gtt aga Met Glu Asp Val Arg 1 5	294
gag aag gtc atg gct gta cct att atg ctg ttc tat ttc agc cta ctc Glu Lys Val Met Ala Val Pro Ile Met Leu Phe Tyr Phe Ser Leu Leu 10 15 20	342
tat aat tot ctg ctt ttt ttg aat cct att ctt ttg ctg agt acc acc Tyr Asn Ser Leu Leu Phe Leu Asn Pro Ile Leu Leu Leu Ser Thr Thr 25 30 35	390
cac cta ctt ctg gga gac aag gct gtg tga a agacatcctc agacgtctca His Leu Leu Gly Asp Lys Ala Val $\star$ 40 $\star$ 45 .	441
tetgetttet catecatetg cacetggatg etggg	476

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tttctagacg tgtgtgtgt tatgtgtacg catgtgtgtg tatgcacaag tagttttggg	180
ttototttto ttggtggtgt acagaagggt agtcaaagco cgactcatga tccctaacto	240
gagtetttta atgggattgt gteetaaetg caaaaeeege eteaeeaaet ttgttataaa	300
ctccccgggt ttatagggac agtcatctac tgtcccttcc taacagcatg gtgcagaaac	360
actccataa atg agt ctt gtg ttg aat cag att gaa tta agt gag aaa Met Ser Leu Val Leu Asn Gln Ile Glu Leu Ser Glu Lys 1 5 10	408
gga atg gcg gtg aaa aat gtg gct tta gtc atc aca tgg gcc tac ggg Gly Met Ala Val Lys Asn Val Ala Leu Val Ile Thr Trp Ala Tyr Gly 15 20 25	456
ttt gtg aaa gta aca ttg agt ctc ctt gtg ttc tgt gtg tac tgc atg Phe Val Lys Val Thr Leu Ser Leu Leu Val Phe Cys Val Tyr Cys Met 30 35 40 45	504
tat gtc atc ttg cat cta agg atg tat att acc cat aaa gga gca tgc Tyr Val Ile Leu His Leu Arg Met Tyr Ile Thr His Lys Gly Ala Cys 50 55 60	552
aga cac atg agt gca tot tgg ott gco act aac tgo otg tgg oot tgg Arg His Met Ser Ala Ser Trp Leu Ala Thr Asn Cys Leu Trp Pro Trp 65 70 75	600
ggc tgt cac tca act ttt cat ctg gaa att gag aat aat aat act att Gly Cys His Ser Thr Phe His Leu Glu Ile Glu Asn Asn Asn Thr Ile 80 85 90	648
atc ctt ctg gaa ttg tgt gca taa atgcacaggg cctggctcat aaaaagtact Ile Leu Leu Glu Leu Cys Ala * 95 100	702
cagtgaggge caggegeggt ggegeaegee tgtaateeea geaetttggg aggeegaggg	762
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ttc ctg cgg cgg ctg ctg gcg gag gag agc cgg cgc tcc acc ccc gtg

Phe Leu Arg Arg Leu Leu Ala Glu Glu Ser Arg Arg Ser Thr Pro Val

5 10 15 20

Met Cys Gly Arg

ggg cgc ctc ttg ctt ccc gtg ctc ctg gga ttc cgc ctt gtg ctg ctg
Gly Arg Leu Leu Pro Val Leu Leu Gly Phe Arg Leu Val Leu Leu
25
389

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tgt cac acc cag cag ccg ggc tgc aag gct gcc tgc ttc gat gcc ttc

Cys His Thr Gln Gln Pro Gly Cys Lys Ala Ala Cys Phe Asp Ala Phe

55 60 65

cac ccc ctc tcc ccg ctg cgt ttc tgg gtc ttc cag gtc atc ttg gtg

His Pro Leu Ser Pro Leu Arg Phe Trp Val Phe Gln Val Ile Leu Val

70 75 80

gct gta ccc agc gcc ctc tat atg ggt ttc act ctg tat cac gtg atc

Ala Val Pro Ser Ala Leu Tyr Met Gly Phe Thr Leu Tyr His Val Ile

85 90 95 100

tgg cac tgg gaa tta tca gga aag ggg aag gag gag acc ctg atc . 629
Trp His Trp Glu Leu Ser Gly Lys Gly Lys Glu Glu Glu Thr Leu Ile
105 110 115

cag gga cgg gag ggc aac aca gat gtc cca ggg gct gga agc ctc agg 677 Gln Gly Arg Glu Gly Asn Thr Asp Val Pro Gly Ala Gly Ser Leu Arg 120 125 130

ctg ctc tgg gct tat gtg gct cag ctg ggg gct cgg ctt gtc ctg gag 725 Leu Leu Trp Ala Tyr Val Ala Gln Leu Gly Ala Arg Leu Val Leu Glu 135 140 145

ggg gca gcc ctg ggg ttg cag tac cac ctg tat ggg ttc cag atg ccc 773
Gly Ala Ala Leu Gly Leu Gln Tyr His Leu Tyr Gly Phe Gln Met Pro
150
150
160

agc tcc ttt gca tgt cgc cga gaa cct tgc ctt ggt agt ata acc tgc 821 Ser Ser Phe Ala Cys Arg Arg Glu Pro Cys Leu Gly Ser Ile Thr Cys 165 170 175 180

aat ctg tcc cgc ccc tct gag aag acc att ttc cta aag acc atg ttt

Asn Leu Ser Arg Pro Ser Glu Lys Thr Ile Phe Leu Lys Thr Met Phe

gga gtc agc ggt ttc tgt ctc ttg ttt act ttt ttg gag ctt gtg ctt 917 Gly Val Ser Gly Phe Cys Leu Leu Phe Thr Phe Leu Glu Leu Val Leu 200 205 210

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					_	-	_		_	aaa Lys	_	1013
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W O 01/33437			
65	70	75	

		65					70					75				
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gtc Val 95	gcc Ala	tgc Cys	gac Asp	tgc Cys	ctg Leu 100	ctg Leu	cag Gln	gag Glu	cac His	ttc Phe 105	tac Tyr	ctg Leu	cgg Arg	cgc Arg	agg Arg 110	576
cgg Arg	cgc Arg	gtg Val	cac His	cgt Arg 115	tac Tyr	gag Glu	gag Glu	agc Ser	gag Glu 120	gtc Val	ata Ile	tct Ser	ttg Leu	ccc Pro 125	ttc Phe	624
ctg Leu	gat Asp	cag Gln	ctg Leu 130	gtg Val	tca Ser	acc Thr	ctc Leu	gtg Val 135	ggc Gly	ctc Leu	ctc Leu	agc Ser	cca Pro 140	cac His	aac Asn	672
ccg Pro	gcc Ala	ctg Leu 145	gcc Ala	gct Ala	gcc Ala	gcc Ala	ctc Leu 150	gat Asp	tat Tyr	aga Arg	tgc Cys	cca Pro 155	gtt Val	cat His	ttt Phe	720
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cga Arg 175	Ile	gat Asp	gac Asp	ttg Leu	cga Arg 180	tac Tyr	cag Gln	ata Ile	gat Asp	gat Asp 185	Lys	cca Pro	aac Asn	aac Asn	cag Gln 190	816
att Ile	cga Arg	ata Ile	tcc Ser	aag Lys 195	Gln	ctc Leu	gca Ala	gag Glu	ttt Phe 200	vai	Pro	ttg Leu	gat Asp	tat Tyr 205	261	864
gtt Val	cct Pro	ata Ile	gaa Glu 210	Ile	ccc Pro	act Thr	ata Ile	aaa Lys 215	Cys	aaa Lys	cca Pro	gac Asp	aaa Lys 220	Let	cca Pro	912
tta Leu	tto Phe	: aaa : Lys 225	Arg	cag Glr	, tat Tyr	gaa Glu	aac Asn 230	His	ata Ile	ttt Phe	gtt Val	ggc L Gly 235	Ser	aaa Lys	act Thr	960
gca Ala	a gat a Asp 240	Pro	tgo Cys	tgt Cys	tac Tyr	ggt Gl <sub>y</sub> 245	His	acc Thr	cag Glr	ttt Phe	cat His 25	s Lev	g tta 1 Leu	cct Pro	gac Asp	1008
aaa Lys 25	s Let	a aga 1 Arg	a agg g Arg	g gaa g Glu	a agg u Arg 260	, Le	ttg Leu	g aga n Arg	a caa g Glr	a aad n Asi 26!	а Су	t gci s Ala	gat a Asp	caq Gli	g ata n Ile 270	1056
ga: Gl:	a gti u Val	t gt l Va	t ttt 1 Phe	aga Arg 27	g Ala	aat Asi	gct Ala	att a Ile	gca Ala 280	a Se	c ct r Le	t tt u Ph	t gci e Ala	t tgg a Trj 28	g act p Thr 5	1104
G1	a gca y Ala	a ca a Gl	a gci n Ala 29	a Me	g tat t Ty	c caa	a gga n Gly	29!	e Tr	g ag p Se	t ga r Gl	a gc u Al	a ga a As 30	p Va	t act l Thr	1152
cg Ar	a cc g Pr	t tt o Ph 30	e Va	c tc l Se	c caç r Glı	g gc	t gtg a Val	l Il	c ac	a ga r As	t gg p Gl	a aa y Ly 31	s Ty	c tt r Ph	t tcc e Ser	1200
tt Ph	t tt e Ph	c tg e Cy	c ta	c ca r Gl	g cta n Le	a aa u As	t act	t tt	g gc u Al	a ct a Le	g ac u Th	t ac	a ca r Gl	a gc n Al	t gat a Asp	1248

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tcaaattcat cactgaaaga t	ttaatttta gttacctttt	gttgatttaa aaataatt	gc 1625
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1726

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cacaaatgtg ttcagaagtt ttacttgtga tagcaaaaat taaaaacaag tcgacttttc	780
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ataaaaaaat aatacatttg gtacattcca ctacacga atg agt ctc aaa aga Met Ser Leu Lys Arg 1 5	893
att att ctg aga aaa gat tta aga ttt aaa aaa agt atc aca ctg cat Ile Ile Leu Arg Lys Asp Leu Arg Phe Lys Lys Ser Ile Thr Leu His 10 15 20	941
gaa caa ttt cat gta ttt aaa ttc tac aaa aag aca caa acc agt agc Glu Gln Phe His Val Phe Lys Phe Tyr Lys Lys Thr Gln Thr Ser Ser 25 30 35	989
gtg att gtt gag ggg agg aga aga ggg agg tat tac aaa ggg aca tgt Val Ile Val Glu Gly Arg Arg Arg Gly Arg Tyr Tyr Lys Gly Thr Cys 40 45 50	1037
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agg gca cac aaa cca atc cga ttt gaa aaa cac aac ttt aca ata aat Arg Ala His Lys Pro Ile Arg Phe Glu Lys His Asn Phe Thr Ile Asn 20 25 30	215
gaa gga aac ctg ttc tct atg aat atc cca att gta acg att agg tct Glu Gly Asn Leu Phe Ser Met Asn Ile Pro Ile Val Thr Ile Arg Ser 35 40 45	263
cac cac agg aca agt tgc tac cac aaa tta atc aca tgt gaa cag caa His His Arg Thr Ser Cys Tyr His Lys Leu Ile Thr Cys Glu Gln Gln	311

PCT/US01/02623 WO 01/55437 . 360 act gtc ttt acg aac ata aag agg cat tct aag ttg tag cagacgcctg Thr Val Phe Thr Asn Ile Lys Arg His Ser Lys Leu \* ctctacgaga cattaatgga gtaaaatcct ggagtattac agataaacag ttaaagtgat 420 gaacaagggc tttatggttt gtataaacag aaatataaac aattttgtat ttttctcaat 480 tatatgtaat taaataacgt ttcagggtaa caaagtattg ggtccctttt tttaccagct 540 tattctaaag aggctttgaa taaaggaaat tttgtttctt gcctccaaga aagagccccc 600 eccecece tecaaatttt gatagaaaaa aaatttgnee agageetega eeeeeeeee 659 <210> 83 <211> 653 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (147) .. (308) <400> 83 ccggtccgga attcccgggt cgacccacgc gtccgatttc ctaaaacttt attcctctaa 60 acatettete aatteeceag atettgtttt agttgtagag geecaaagta gageteteta 120 aacaaaggct teeteagtge tgtaaa atg aat ttg tat ete ttt get gtt ete 173 Met Asn Leu Tyr Leu Phe Ala Val Leu 1 221 ttc ttt tat gta ttt cta cat ata aaa atc atc ttt att tgt ttt gct Phe Phe Tyr Val Phe Leu His Ile Lys Ile Ile Phe Ile Cys Phe Ala 15 10 269 act aaa tgg cat aat tta ttt tcg aaa ttc agt tat ttt tgt att ttg Thr Lys Trp His Asn Leu Phe Ser Lys Phe Ser Tyr Phe Cys Ile Leu 30 cat gtt aag gct cta agc ctt aac tta ggg tct ggg taa atatgaactc 318 His Val Lys Ala Leu Ser Leu Asn Leu Gly Ser Gly \* caagacteet egaaaatagt gtagaaataa tagcaaaatt aaagatgttt gtatteeetg 378 438 tgaatttatt ttttctttca ttcaacacag aatgtgtatc tagtacgtgc taggcattat aaatttagca gtgaacaaag atgataaaat ctcagctctc ctggagccaa cgttctagtg 498 558 aaaaatttot otttottota otttttotgt tgacattoat atgggotaac aatgtaccco gagggctggg gattataaag gagaagaaag gtgggggacc cggctcagct ggtaaaatgg 618

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653

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tttttcttca ttttttatgg aatgtaaagc tcatcc atg tgt aca tta ttc atg Met Cys Thr Leu Phe Met 1 5	174
cat tta ctt ttc tgc cac ctc caa agc att caa tta aag cag gaa tta His Leu Leu Phe Cys His Leu Gln Ser Ile Gln Leu Lys Gln Glu Leu 10 15 20	222
agg ctc aac tat ctt act tta aca cag ttt tgg cag aga tgt tac agt Arg Leu Asn Tyr Leu Thr Leu Thr Gln Phe Trp Gln Arg Cys Tyr Ser 25 30 35	270
gag atg att ttt ttc tgt ctg tca aag gtg ttt ctt cat gtt ttc caa Glu Met Ile Phe Phe Cys Leu Ser Lys Val Phe Leu His Val Phe Gln 40 45 50	318
gat ggt cta gaa cat cat tta gag taa atttt cattttggag gaaattttta Asp Gly Leu Glu His His Leu Glu * 55 60	370
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aaaagcccaa agggaaaaaa taagtttctt actctgactt tcacacatac tgtgttctat	490
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aatggtttta atgcctttta accttttaaa atttttatgg acaatttaac tggcattttt	610
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<220>

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WO 01/55437	PCT/US01.	/02623
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	tgt ccaggettae ccagaeetat gteacgatet	600
tcattccagc tcttcctgca acctttc		653
Leu Asn Gln Gly Ile Val Leu P	ecc cag atc gta act gga gtt gca gcc Pro Gln Ile Val Thr Gly Val Ala Ala 15 20	701
aac ctt gtc aat gcc ctc gcc a Asn Leu Val Asn Ala Leu Ala A 25	aac tat ctg ttt ctc cat caa ctg cat Asn Tyr Leu Phe Leu His Gln Leu His 35	749
ctt ggg gtg ata ggc tct gca c Leu Gly Val Ile Gly Ser Ala I 40 45	ctg gca aac ttg att tcc cag tac acc Leu Ala Asn Leu Ile Ser Gln Tyr Thr 50	797
ctg gct cta ctc ctc ttt ctc t Leu Ala Leu Leu Leu Phe Leu 7 60	tac atc ctc ggg aaa aaa ctg cat caa Tyr Ile Leu Gly Lys Lys Leu His Gln 65	845
Ala Thr Trp Gly Gly Trp Ser 1 75	ctc gag tgc ctg cag gac tgt gcc tcc Leu Glu Cys Leu Gln Asp Cys Ala Ser 80 85	893
ttc ctc cgc ctg gcc atc ccc of Phe Leu Arg Leu Ala Ile Pro	agc atg ctc atg ctg tgc atg gag tgg Ser Met Leu Met Leu Cys Met Glu Trp 95	941
tgg gcc tat gag gtc ggg agc Trp Ala Tyr Glu Val Gly Ser 105	ttc ctc agt ggc atc ctc ggc atg gtg Phe Leu Ser Gly Ile Leu Gly Met Val 115	989
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gct ctg ggt gct gga gac atg Ala Leu Gly Ala Gly Asp Met 155	gag cag gca cgg aag tcc tct acc gtt Glu Gln Ala Arg Lys Ser Ser Thr Val 160 165	1133
tcc ctg ctg att aca gtg ctc Ser Leu Leu Ile Thr Val Leu 170	ttt gct gta gcc ttc agt gtc cta ctg Phe Ala Val Ala Phe Ser Val Leu Leu 175 . 180	1181
tta agc tgt aag gat cac gtg Leu Ser Cys Lys Asp His Val 185 190	ggg tac att ttt act acc gac cga gac Gly Tyr Ile Phe Thr Thr Asp Arg Asp 195	1229
atc att aat ctg gtg gct cag Ile Ile Asn Leu Val Ala Gln 200 205	gtg gtt cca att tat gct gtt tcc cac Val Val Pro Ile Tyr Ala Val Ser His 210 215	1277
ctc ttt gaa gct ctt gct tgc Leu Phe Glu Ala Leu Ala Cys	e acg agt ggt ggt gtt ctg agg ggg agt Thr Ser Gly Gly Val Leu Arg Gly Ser	1325

gga aat cag aag gtt gga gcc att gtg aat acc att ggg tac tat gtg 1373 Gly Asn Gln Lys Val Gly Ala Ile Val Asn Thr Ile Gly Tyr Tyr Val 235 get ggc etc ecc ate ggg ate geg etg atg ttt gea acc aca ett gga 1421 Ala Gly Leu Pro Ile Gly Ile Ala Leu Met Phe Ala Thr Thr Leu Gly 250 255 gtg atg ggt ctg tgg tca ggg atc atc atc tgt aca gtc ttt caa gct 1469 Val Met Gly Leu Trp Ser Gly Ile Ile Ile Cys Thr Val Phe Gln Ala 265 270 gtg tgt ttt cta ggc ttt att att cag cta aat tgg aaa aaa gcc tgt 1517 Val Cys Phe Leu Gly Phe Ile Ile Gln Leu Asn Trp Lys Lys Ala Cys 285 290 1567 Gln Gln Gly Ala Leu Lys Thr Leu Lys Glu Phe \* 300 aagacaggcg agcctcagtc agatcagcag atgcgccaag aagaaccttt gccggaacat 1627 ccacaggacg gcgctaaatt gtccaggaaa cagctggtgc tgcggcgagg gcttctgctc 1687 ctgggggtct tcttaatctt gctggtgggg attttagtga gattctatgt cagaattcag tgacgtggta ggaaagaaag tcaggtcaag tgatgctttt gagcttacac acaattcgca 1807 ggccgaatta cgccactctt t 1828

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<221> misc\_feature

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WO 01/55437 PCT/US01/0	2623
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act ttc tct ctc ttg gat cta cca cca gta aat gaa tat gac atg tat Thr Phe Ser Leu Leu Asp Leu Pro Pro Val Asn Glu Tyr Asp Met Tyr 50 55 60	372
atc aga aac ttt gga aaa aaa aaa agg ggg ggc cgt ttt aaa gga Ile Arg Asn Phe Gly Lys Lys Lys Lys Arg Gly Gly Arg Phe Lys Gly 65 70 75 80	420
tcc agg ttt acg aac gcg ggc tgg caa cgt aaa agt ttt ttt atg ggg Ser Arg Phe Thr Asn Ala Gly Trp Gln Arg Lys Ser Phe Phe Met Gly 85 90 95	468
ccc cct aaa tcc att cca ggg gcc ggg gtt taa caacgggg ggacgggaaa Pro Pro Lys Ser Ile Pro Gly Ala Gly Val * 100 105	519
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cca gcg tcg ccc acg acc gca gca gcc tcg ccc agc gtc tcc gtg atc Pro Ala Ser Pro Thr Thr Ala Ala Ala Ser Pro Ser Val Ser Val Ile

ccc gag ggc agc ccc act gcc atg gag cag cct gtg ttc ctg atg aca

WO 01/55437 PCT/US01/02623 Pro Glu Gly Ser Pro Thr Ala Met Glu Gln Pro Val Phe Leu Met Thr act ged get dag ged atd tet ggd ttd ttd gtg tgg acg ged etg etc 316 Thr Ala Ala Gln Ala Ile Ser Gly Phe Phe Val Trp Thr Ala Leu Leu atc aca tgc cac cag atc tac atg cac ctg cgc tgc tac agc tgc ccc 364 Ile Thr Cys His Gln Ile Tyr Met His Leu Arg Cys Tyr Ser Cys Pro aac gag cag cgc tac atc gtg cgc atc ctc ttc atc gtg ccc atc tac 412 Asn Glu Gln Arg Tyr Ile Val Arg Ile Leu Phe Ile Val Pro Ile Tyr ged ttt gad ted tgg etc age etc etc ttc ttc acc aac gad cag tac 460 Ala Phe Asp Ser Trp Leu Ser Leu Leu Phe Phe Thr Asn Asp Gln Tyr 100 tac gtg tac ttc ggc acc gtc cgc gac tgc tat gag gcc ttg gtc atc 508 Tyr Val Tyr Phe Gly Thr Val Arg Asp Cys Tyr Glu Ala Leu Val Ile 115 tat aat ttc ctg agc ctg tgc tat gag tac cta gga gga gaa agt tcc 556 Tyr Asn Phe Leu Ser Leu Cys Tyr Glu Tyr Leu Gly Gly Glu Ser Ser 130 atc atg tcg gag atc aga gga aaa ccc att gag tcc agc tgt atg tat 604 Ile Met Ser Glu Ile Arg Gly Lys Pro Ile Glu Ser Ser Cys Met Tyr 140 150 ggc acc tgc tgc ctc tgg gga aag act tat tcc atc gga ttt ctg agg 652 Gly Thr Cys Cys Leu Trp Gly Lys Thr Tyr Ser Ile Gly Phe Leu Arg 170 ttc tgc aaa cag gcc acc ctg cag ttc tgt gtg gtg aag cca ctc atg 700 Phe Cys Lys Gln Ala Thr Leu Gln Phe Cys Val Val Lys Pro Leu Met 175 gcg gtc agc act gtg gtc ctc cag gcc ttc ggc aag tac cgg gat ggg 748 Ala Val Ser Thr Val Val Leu Gln Ala Phe Gly Lys Tyr Arg Asp Gly 195 gac ttt gac gtc acc agt ggc tac ctc tac gtg acc atc atc tac aac 796 Asp Phe Asp Val Thr Ser Gly Tyr Leu Tyr Val Thr Ile Ile Tyr Asn 210 atc tcc gtc age ctg gcc ctc tac gcc ctc ttc ctc ttc tac ttc gcc 844 Ile Ser Val Ser Leu Ala Leu Tyr Ala Leu Phe Leu Phe Tyr Phe Ala 230 acc egg gag etg etc age ecc tac age ecc gte etc aag tte tte atg 892 Thr Arg Glu Leu Leu Ser Pro Tyr Ser Pro Val Leu Lys Phe Phe Met 245 gtc aag tcc gtc atc ttt ctt tcc ttc tgg caa ggc atg ctc ctg gcc 940 Val Lys Ser Val Ile Phe Leu Ser Phe Trp Gln Gly Met Leu Leu Ala 255

988

1036

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Ile Leu Glu Lys Cys Gly Ala Ile Pro Lys Ile His Ser Ala Arg Val

tog gtg ggc gag ggc acc gtg gct gcc ggc tac cag gac ttc atc atc

W	J U1/5	543/												1	PCT/US0	1/02623
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tgt Cys 300	gtg Val	gag Glu	atg Met	ttc Phe	ttt Phe 305	gca Ala	gcc Ala	ctg Leu	gcc Ala	ctg Leu 310	cgg Arg	cac His	gcc Ala	ttc Phe	acc Thr 315	1084
tac Tyr	aag Lys	gtc Val	tat Tyr	gct Ala 320	gac Asp	aag Lys	agg Arg	ctg Leu	gac Asp 325	gca Ala	caa Gln	ggc Gly	cgc Arg	tgt Cys 330	gcc Ala	1132
ccc Pro	atg Met	aag Lys	agc Ser 335	atc Ile	tcc Ser	agc Ser	agc Ser	ctc Leu 340	aag Lys	gag Glu	acc Thr	atg Met	aac Asn 345	ccg Pro	cac His	1180
gac Asp	atc Ile	gtg Val 350	cag Gln	gac Asp	gcc Ala	atc Ile	cac His 355	aac Asn	ttc Phe	tca Ser	cct Pro	gcc Ala 360	tac Tyr	cag Gln	cag Gln	1228
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Gly Lys Lys Val Thr Leu Leu Gln Lys Cys Ala Trp Leu Leu Leu
5 10 15

WO 01/55437 PCT/US01/02623 gtt tgc tgc cta ttc act ggc att aag tac ctg aac aaa tgt ttt atc Val Cys Cys Leu Phe Thr Gly Ile Lys Tyr Leu Asn Lys Cys Phe Ile 25 aca gac agg gaa ctg ttg agg gat gtt cac aat gca ttg aac atc ctt 262 Thr Asp Arg Glu Leu Leu Arg Asp Val His Asn Ala Leu Asn Ile Leu 40 agg cat aat ttt tat gtg aac tgg gca tcc tta aat aca ttc tga ctc 310 Arg His Asn Phe Tyr Val Asn Trp Ala Ser Leu Asn Thr Phe \* 55 catgatcaga ttaccagaaa gtgcaggtcc cactcactat cttgattcag catctcccat 370 ctggccaaag ttgaatttta cattgagttg gatggtgata aatatgctta gcaaaagtat 430 attcgttgtt tctgaagttc tctgtgctga taaacactgg ctgggactag ggaagtgggc 490 cccaaataaa acaatagcaa taatccccaa actggttggg gaagggcagg ctttatttt 550 gtgcactctt aaggggaaat gtaagttaaa ctttccaccc ccccccaaag gtttttgctt gtttggaggg ccccaacctt tgggggcccc tcccaatgcc ttaatt 656 <210> 90 <211> 646 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (263)..(553) <400> 90 ccggtccgga attcccgggt cgacccacgc gtccgcaact atcttatttc cttatcatgc 60 acaagttaaa tgttagactg aggagtaggt gagttatccc caaggaagta aaatgatgtt 120 aattttcttg aggtcacatg aattgtgagt agctgaatgc tactgtgaat tctgggcagc 180 ccgaccacag agcctgaact cttaaatatt atactgtatt aacttgacat gtttataaaa 240 gtaacaatta catgetacet ga atg eec tea gta gtt ttg aac atg gtg caa 292 Met Pro Ser Val Val Leu Asn Met Val Gln ctg ttt atc cct ata cta aaa ttc caa tta ggc tat tct gtt ttg agt 340 Leu Phe Ile Pro Ile Leu Lys Phe Gln Leu Gly Tyr Ser Val Leu Ser 15 ctt tgt aat cat gtt tta gaa ttt ttg ttt cct tcc tca ttg tca ggc 388 Leu Cys Asn His Val Leu Glu Phe Leu Phe Pro Ser Ser Leu Ser Gly 30 35 ate tit tet tee tee ett eec ete ett ett eec tie eet ett tet ett 436 Ile Phe Ser Ser Leu Pro Leu Leu Pro Phe Pro Leu Ser Leu 50 ecc tet ett ecc ect tet ett tet ect tet ett aga gte ttg ete tge 484 Pro Ser Leu Pro Pro Ser Leu Phe Pro Ser Leu Arg Val Leu Leu Cys

cac cca cac tgg agt gta gcc tca aac tcc tgg gct gta gcc atc ctc His Pro His Trp Ser Val Ala Ser Asn Ser Trp Ala Val Ala Ile Leu 75 80 85 90	532
cta cct cag cct cct gag tag ct gggactgcaa gtgtatacca ctatgcctgg Leu Pro Gln Pro Pro Glu * 95	585
ctaatttaaa aaaatttaaa atttttttt ttttggaaaa acaaaagcct cctttgttgc	645
c	646
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the thirty and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the same and the	
agatttaatt ttttaaatgt catttttctt gcatctcatc aaatatactt tcatacacta	120
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa  Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys  1 5 10	120 167
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys	
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa  Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys  1 5 10  tgc aaa cct ttg gac act gac tca aca tct gga gat att ttt tct ggt Cys Lys Pro Leu Asp Thr Asp Ser Thr Ser Gly Asp Ile Phe Ser Gly	167
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys  1 5 10  tgc aaa cct ttg gac act gac tca aca tct gga gat att ttt tct ggt Cys Lys Pro Leu Asp Thr Asp Ser Thr Ser Gly Asp Ile Phe Ser Gly 15 20 25 30  tct tat ggc tgg tgt tct cct aca gct ctc tac gag cag tct tgt gaa Ser Tyr Gly Trp Cys Ser Pro Thr Ala Leu Tyr Glu Gln Ser Cys Glu	167 215
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys 1 5 10  tgc aaa cct ttg gac act gac tca aca tct gga gat att ttt tct ggt Cys Lys Pro Leu Asp Thr Asp Ser Thr Ser Gly Asp Ile Phe Ser Gly 15 20 25 30  tct tat ggc tgg tgt tct cct aca gct ctc tac gag cag tct tgt gaa Ser Tyr Gly Trp Cys Ser Pro Thr Ala Leu Tyr Glu Gln Ser Cys Glu 35 40 45  gcc cac aag cac cga ggg aac cca tcc ggg ctt tac tat att gat gca Ala His Lys His Arg Gly Asn Pro Ser Gly Leu Tyr Tyr Ile Asp Ala	167 215 263
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys 1 5 10  tgc aaa cct ttg gac act gac tca aca tct gga gat att ttt tct ggt Cys Lys Pro Leu Asp Thr Asp Ser Thr Ser Gly Asp Ile Phe Ser Gly 15 20 25 30  tct tat ggc tgg tgt tct cct aca gct ctc tac gag cag tct tgt gaa Ser Tyr Gly Trp Cys Ser Pro Thr Ala Leu Tyr Glu Gln Ser Cys Glu 35 40 45  gcc cac aag cac cga ggg aac cca tcc ggg ctt tac tat att gat gca Ala His Lys His Arg Gly Asn Pro Ser Gly Leu Tyr Tyr Ile Asp Ala 50 55 60  gat gga agt ggc ccc ctg gga cca ttt ctt gtg tac tgc aat atg aca Asp Gly Ser Gly Pro Leu Gly Pro Phe Leu Val Tyr Cys Asn Met Thr	167 215 263 311
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys 1 5 10  tgc aaa cct ttg gac act gac tca aca tct gga gat att ttt tct ggt Cys Lys Pro Leu Asp Thr Asp Ser Thr Ser Gly Asp Ile Phe Ser Gly 15 20 25 30  tct tat ggc tgg tgt tct cct aca gct ctc tac gag cag tct tgt gaa Ser Tyr Gly Trp Cys Ser Pro Thr Ala Leu Tyr Glu Gln Ser Cys Glu 35 40 45  gcc cac aag cac cga ggg aac cca tcc ggg ctt tac tat att gat gca Ala His Lys His Arg Gly Asn Pro Ser Gly Leu Tyr Tyr Ile Asp Ala 50 55 60  gat gga agt ggc ccc ctg gga cca ttt ctt gtg tac tgc aat atg aca Asp Gly Ser Gly Pro Leu Gly Pro Phe Leu Val Tyr Cys Asn Met Thr 65 70 75  ggt atg ttg ata atc gtt aga tgc ata gat cag aat aga cca agg aga Gly Met Leu Ile Ile Val Arg Cys Ile Asp Gln Asn Arg Pro Arg Arg	167 215 263 311

atttettett tgeetgggtt ggattatagg caagatteaa tgetetgeea aggeatetet: ctagetecta eactecteat aatacatetg tteatgtgea teatgataaa atacaaacet ctgattcggt gatttacatg ctttctgtat ttagaaaaaa cagaggtgtt taaaaaatgct 699 759 aaqaaataac ataqatatgt taatgttcta tgtgcatctt aaataattta gtgattttta tgtcatataa ttttttcata accaaagaaa cttgattatt tctcgtgctt tagatattag 819 879 aaatgaacac tgcttgggct gcgcatggtg gctcgcgcct gtaatctcag cactttggga ggccgaggcg ggcggatcgc gagatcgaga gatcgagacc atcctggcca atgtggtgaa 939 999 accocgtoto tactgaaaat gcaaaaatta gctgggcatg gtggcgcccg cacctgtagt cccagctact tgggaggctg aggcgggagg atcccttgaa ccanggaggn cgaggttgca 1059 gtgagccagg attgcgccat tgcactccag cctggtgaca gagcaagact gcatctcaaa 1119 1126 aaaaaaa

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Ala Leu \*

ctgagggtac acagtgtggc tgctgcctgg tgccctgtga gggagcaggg tcccttctag 489 ctqqqaqcaa tqgcgcatgc ctgtaatcct agcactttgg gaggctgagg caggagtatc gettgagete aggagttega gaccageetg gacaacatga egaaaceeca tetetaennn 609 669 tttttaaaaa acacaatttt ttcccggggg gtgagaaaaa ttatttttt tttttgggg ccctaaaatt tttttctggg ggccgctttt tttacacggg gggggagggg gaaagnnncg 729 789 ngngggcett egttgeegeg ggeegngtgg egeegggeeg ggtettgtte gttggggggg cetgettett tttettteg etgtggetee ggeggttgtg ggegggnege gttggeeegg 849 904 gagttggggt ggccacgact ggtaaattgg tcgggaggag acctctatgg ggctg

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<213> Homo sapiens

<220>
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517

Phe Glu Asn Ile Leu Met Tyr Thr His Ala Phe Ile Ile Cys Phe Cys

aac aga cag tgg ctt ttt aaa agt aat agt gaa agt aat ctt agt agc

Asn Arg Gln Trp Leu Phe Lys Ser Asn Ser Glu Ser Asn Leu Ser Ser

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95	100	105	110
aat gtt aat tta ttt Asn Val Asn Leu Phe 115		tttc aggtacgcaa	aaggaggaga 569
tgatttcctt taaaaact	ca gctttgaata gtto	gtgtta tctggtata	t ctgaaatatt 629
cagaaatgtt aaaacagt	tt ttgtttgcct ttgo	etgttaa gtttgaaac	c tcttagtgct 689
ttcaattgat aatcctgg	aa accaacctca gtat	tgtagt attacatag	a ttattggagt 749
tttatagtct tgaaaata	aa gggctaatag ccat	agatat atcgctgac	a ctaaaatagc 809
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ctcactctga ccctgata			
aag atg cag ctc ca Met Gln Leu Hi 1	t ggc aaa gga tct s Gly Lys Gly Ser 5	caa gat ccc agc Gln Asp Pro Ser 10	acc aag ggc 168 Thr Lys Gly 15
cac ata aaa gct ttg His Ile Lys Ala Leu 20	Gln Thr Val Thr	tcc ttt ctt ctg t Ser Phe Leu Leu L 25	ta tgt gcc 216 eu Cys Ala 30
att tac ttt ctg tcc Ile Tyr Phe Leu Ser 35			
gaa aag caa cct gtc Glu Lys Gln Pro Val 50			
cct tca acc cac cca Pro Ser Thr His Pro 65			

cag att ttt ctt tca gtt ttg cgg cat gtg agg tac tgg gtg aaa gac Gln Ile Phe Leu Ser Val Leu Arg His Val Arg Tyr Trp Val Lys Asp 80 85 90 95

456
516
576
636
696
756
816
876
931

<210> 95 <211> 1278 <212> DNA <213> Homo sapiens <220> <221> CDS

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atg gct

ctc ggg Leu Gly 115	gcg gca Ala Ala	a cag a Gln	ttc Phe 120	cag Gln	gga Gly	Gly ggg	gag Glu	ctg Leu 125	gca Ala	ctg Leu	tct Ser	gca Ala	ttc Phe 130	439
tta gtg Leu Val	cta gta Leu Va	a ttt l Phe 135	ctg Leu	tgg Trp	ctg <b>Le</b> u	cac His	agc Ser 140	tta Leu	cga Arg	aga Arg	ctc Leu	ttc Phe 145	gag Glu	487
tgc ctc Cys Leu	tac gt Tyr Va 15	l Ser	gtc Val	ttc Phe	tcc Ser	aat Asn 155	gtc Val	atg Met	att Ile	cac His	gtc Val 160	gtg Val	cag Gln	535
tac tgt Tyr Cys	ttt gg Phe Gl	a ctt y Leu	gtc Val	tat Tyr	tat Tyr 170	gtc Val	ctt Leu	gtt Val	ggc Gly	cta Leu 175	act Thr	gtg Val	ctg Leu	583
agc caa Ser Gln 180	gtg cc Val Pr	a atg o Met	gat Asp	ggc Gly 185	agg Arg	aat Asn	gcc Ala	tac Tyr	ata Ile 190	aca Thr	Gly aaa	aaa Lys	aat Asn	631
cta ttg Leu Leu 195	atg ca Met Gl	a gca n Ala	cgg Arg 200	tgg Trp	ttc Phe	cat His	att Ile	ctt Leu 205	gly ggg	atg Met	atg Met	atg Met	ttc Phe 210	679
atc tgg Ile Trp	tca tc Ser Se	t gcc r Ala 215	cat His	cag Gln	tat Tyr	aag Lys	tgc Cys 220	cat His	gtt Val	att Ile	ctc Leu	ggc Gly 225	aat Asn	727
ctc agg Leu Arg	aaa aa Lys As 23	n Lys	gca Ala	gga Gly	gtg Val	gtc Val 235	att Ile	cac His	tgt Cys	aac Asn	cac His 240	agg Arg	atc Ile	775
cca ttt Pro Phe	gga ga Gly As 245	c tgg p Trp	ttt Phe	gaa Glu	tat Tyr 250	gtt Val	tct Ser	tcc Ser	cct Pro	aac Asn 255	tac Tyr	tta Leu	gca Ala	823
gag ctg Glu Leu 260	atg at Met Il	c tac e Tyr	gtt Val	tcc Ser 265	atg Met	gcc Ala	gtc Val	acc Thr	ttt Phe 270	Gly	ttc Phe	cac His	aac Asn	871
tta act Leu Thr 275	tgg tg Trp Tr	g cta p Leu	gtg Val 280	gtg Val	aca Thr	aat Asn	gtc Val	ttc Phe 285	ttt Phe	aat Asn	cag Gln	gcc Ala	ctg Leu 290	919
tct gcc Ser Ala	ttt ct Phe Le	c ago u Ser 295	His	caa Gln	ttc Phe	tac Tyr	aaa Lys 300	agc Ser	aaa Lys	ttt Phe	gtc Val	tct Ser 305	tac Tyr	967
ccg aag Pro Lys		g Lys					Phe				g tt	aacc	tcag	1017
tcatgaa	gaa tgc	aaacc	ag g	tgat	ggtt	t ca	atgc	ctaa	gga	cagt	gaa	gtct	ggagtc	1077
caaagta	cag ttt	cagca	aa g	ctgt	ttga	a ac	tctc	catt	cca	tttc	tat	accc	cacaag	1137
ttttcac														1197
agaataa	ata cta	atggo	ag a	tctg	cctc	g tg	ccga	attc	gaa	tcga	tgg	gatc	ctgcaa	1257
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age tac tta gee tgg tac cag cag aaa eet gge cag Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln 185	gct ccc agg ctc 749 Ala Pro Arg Leu 195
ctc atc tat ggt gca tcc agc agg gcc act ggc atc Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile 200 205	cca gac agg ttc 797 Pro Asp Arg Phe 210
agt ggc agt ggg tct ggg aca gac ttc act ctc acc Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr 215	atc agc aga ctg 845 Ile Ser Arg Leu 225
gag cct gaa gat ttt gca gtg tat tac tgt cag cag Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln 230 235 240	Thr Gly Arg Ile
ccg ccg acg ttc ggc caa ggg acc aag gtg gaa atc Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile 245 250 255	aaa cga act gtg 941 Lys Arg Thr Val 260
gct gca cca tct gtc ttc atc ttc ccg cca tct gat Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp 265 270	gag cag ttg aaa 989 Glu Gln Leu Lys 275
tct gga act gcc tct gtt gtg tgc ctg ctg aat aac Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn 280 285	ttc tat ccc aga 1037 Phe Tyr Pro Arg 290
gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu 295 300	cca atc ggg taa 1085 Pro Ile Gly * 305
ctcccaggag agtgtcacag agcaggacag caaggacagc acc	tacagee teageageae 1145
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60

gaa att att agt agc ggt ggt acc aca tac tac gca gac tcc gtg aag 413 Glu Ile Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys

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70	75		80	
			aac acg ctg tat Asn Thr Leu Tyr	
			ata tat tac tgt Ile Tyr Tyr Cys 115	
Lys Asp Ile I			gac tac tgg ggc Asp Tyr Trp Gly 130	
	-		tcc agt ggc ggt Ser Ser Gly Gly 145	-
			cag tot coa ggo Gln Ser Pro Gly 160	
			tcc tgc agg gcc Ser Cys Arg Ala	•
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Gln Ala Pro A		<del>_</del>	agc agg gcc act Ser Arg Ala Thr 210	
			aca gac ttc act Thr Asp Phe Thr 225	
-			gtg tat tac tgt Val Tyr Tyr Cys 240	-
			ggg acc aag gtg Gly Thr Lys Val	~ <u>.</u>
			atc ttc ccg cca Ile Phe Pro Pro 275	
Asp Glu Gln L	tg aaa tct gga eu Lys Ser Gly 80	act gcc tct gtt Thr Ala Ser Val 285	gtg tgc ctg ctg Val Cys Leu Leu 290	aat 1037 Asn
aac ttc tat c Asn Phe Tyr P 295	ecc aga gag gcc ro Arg Glu Ala	aaa gta cag tgg Lys Val Gln Trp 300	aag gtg gat aac Lys Val Asp Asn 305	gcc 1085 Ala

acctacagee teageageae ectgaegetg ageaaageag actacgagaa acacaaagte 1200

ctc cca atc ggg taa ctcccaggag agtgtcacag agcaggacag caaggacagc

Leu Pro Ile Gly \*

tacgcctgcg aagtcaccca tcagggcctg agetcgcccg tcacaaagag cttcaacagg 1260 ggagagtgtt agagggagaa gtgcccccac ctgctcctca gttccagcct gaccccctcc 1320 catectttgg cctctgaccc tttttccaca ggggacctac ccctattgcg gtcctccagc 1380 tcatctttca cctcaccccc ctcctcctcc ttggctttaa ttatgctaat gttggaggag 1440 aatgaataaa taaagtgaat etttgeacet gtggtttete tettteetea tttaataatt 1500 attatetgtt gttttaccaa ctactcaatt tetettataa gggactaaat atgtagtcat 1560 cctaaggcgc ataaccattt ataaaaatca tccttcattc tattttaccc tatcatcctc 1620 tgcaagacag tecteectea aacceacaag cettetgtee teacagteee etgggeeatg 1680 gtaggagaga cttgcttcct tgttttcccc tcctcagcaa gccctcatag tccttt 1736

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Ser Ile Ser Gly Ser Ser Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys

ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat ctg

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu

caa atg aac agc ctg aga gcc gag gac acg gcc gta tat tac tgt gcg

90

95

461

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	tcg Ser															605
_	gac Asp 150		_	_		_					_		-		-	653
	gac Asp															701
	ctg Leu	_			_	-					_		_		_	749
	tat Tyr	-	_				_	_		_					_	797
	agt Ser															845
	gat Asp 230	_		-				_	_			_			-	893
	act Thr															941
	cca Pro		-				_			_		-	_			989
gga Gly	act Thr	gcc Ala	tct Ser 280	gtt Val	gtg Val	tgc Cys	ctg Leu	ctg Leu 285	aat Asn	aac Asn	ttc Phe	tat Tyr	ccc Pro 290	aga Arg	gag Glu	1037
	aaa Lys															1085
cag Gln	gag Glu 310	agt Ser	gtc Val	aca Thr	gag Glu	cag Gln 315	gac Asp	agc Ser	aag Lys	gac Asp	agc Ser 320	acc Thr	tac Tyr	agc Ser	ctc Leu	1133
agc Ser 325	agc Ser	acc Thr	ctg Leu	acg Thr	ctg Leu 330	agc Ser	aaa Lys	gca Ala	gac Asp	tac Tyr 335	gag Glu	aaa Lys	cac His	aaa Lys	ctc Leu 340	1181
tac Tyr	gcc Ala	tgc Cys	gaa Glu	gtc Val 345	acc Thr	cat His	cag Gln	ggc Gly	ctg Leu 350	agc Ser	tcg Ser	ccc Pro	gtc Val	aca Thr 355	aag Lys	1229
agc	ttc	aac	agg	gga	gag	tgt	tag	agg	gagaa	agg	tgcc	ccac	ct g	tcct	cagto	1283

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Ser Phe Asn Arg Gly Glu Cys \* 360

1343 cagootgood cotocoatod titiggootot goodtitito cacaggggad cicocotati geggeeteca geteatettt aceteaeece ecteeeette ettggettta attatgetaa 1403 1463 tgttggagga gaatgaataa ataaagtgaa tetttgcace tgtggtttet etettteete atttaataat tattatetgt tgttttacca actactcaat ttetettata agggactaaa 1523 1583 tatgtagtca tectaaggeg cataaceatt tataaaaate ateetteatt etatttaee ctatcatcct ctgcaagaca gtcctccctc aaacccacaa gccttctgtc ctcacagtcc 1643 cctgggccat ggtaggagag acttgcttcc ttgttttccc ctcctcagca agccctcata 1703 1710 gtccttt

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267 aac ata qtt aaa qca aqa att qaq aqt aca aag aca gtg ata tca aag Asn Ile Val Lys Ala Arg Ile Glu Ser Thr Lys Thr Val Ile Ser Lys 35

20

aga tgt taa teeteea cacagtetgg etgeattgag gatatttete tttgtgeagt 323 Arg Cys \* 45

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ata aga aaa caa ttc aca gct cta gct ggc ttc tgc ttc tgg ttc tgt Ile Arg Lys Gln Phe Thr Ala Leu Ala Gly Phe Cys Phe Trp Phe Cys 10 15 20	283										
ctc ttt acc tta gca gtc ctg agt ctc acc ttg ctt atc tgc aaa ctg Leu Phe Thr Leu Ala Val Leu Ser Leu Thr Leu Leu Ile Cys Lys Leu 25 30 35	331										
agg ata atg cca ttt aaa ctt gaa ggt ttg ttt caa gaa tta aat aaa Arg Ile Met Pro Phe Lys Leu Glu Gly Leu Phe Gln Glu Leu Asn Lys 40 45 50	379										
tca tgg cat atg aag ctc ttg tca caa gat agg gag tta ata aat atg Ser Trp His Met Lys Leu Leu Ser Gln Asp Arg Glu Leu Ile Asn Met 55 60 65 70	427										
ctg ttg ctc tta atg ggc agg tcc taa gtgat ggcttagaaa cctaagattg Leu Leu Leu Met Gly Arg Ser * 75	479										
gaaggcatct tggagatgtt ctggctcaac ctcctaacaa tgcaaaagtt tgtcctaga	ia 539										
cacteetgga agatggatet ttaggetete attagataac ecagggatee cactgtete	:a 599										
aaaggcägte tgtgcatatt tttggtcagg tetaattett aatgataata acacacatt	t 659										
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		,					10										
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ggc Gly 35	tcc Ser	agg Arg	acc Thr	gcc Ala	ttc Phe 40	ttt Phe	ggc Gly	tac Tyr	aca Thr	gtg Val 45	cag Gln	cag Gln	cac His	gac Asp	atc Ile 50		201
agt Ser	ggc Gly	aat Asn	aag Lys	tgg Trp 55	ctg Leu	gtc Val	gtg Val	ggc Gly	gcc Ala 60	cca Pro	ctg Leu	gaa Glu	acc Thr	aat Asn 65	ggc Gly		249
tac Tyr	cag Gln	aag Lys	acg Thr 70	gga Gly	gac Asp	gtg Val	tac Tyr	aag Lys 75	tgt Cys	cca Pro	gtg Val	atc Ile	cac His 80	Gly ggg	aac Asn		297
tgc Cys	acc Thr	aaa Lys 85	ctc Leu	aac Asn	ctg Leu	gga Gly	agg Arg 90	gtc Val	acc Thr	ctg Leu	tcc Ser	aac Asn 95	gtg Val	tcc Ser	gag Glu	•	345
cgg Arg	aaa Lys 100	gac Asp	aac Asn	atg Met	cgc Arg	ctc Leu 105	ggc Gly	ctt Leu	agt Ser	ctc Leu	gcc Ala 110	acc Thr	aac Asn	ccc Pro	aag Lys		393
gac Asp 115	aac Asn	agc Ser	ttc Phe	ctg Leu	gcc Ala 120	tgc Cys	agc Ser	ccc Pro	ctc Leu	tgg Trp 125	tct Ser	cat His	gag Glu	tgt Cys	999 Gly 130		441
agc Ser	tcc Ser	tac Tyr	tac Tyr	acc Thr 135	aca Thr	Gly	atg Met	tgt Cys	tca Ser 140	aga Arg	gtc Val	aac Asn	tcc Ser	aac Asn 145	ttc Phe		489
agg Arg	ttc Phe	tcc Ser	aag Lys 150	acc Thr	gtg Val	gcc Ala	cca Pro	gct Ala 155	ctc Leu	caa Gln	agg Arg	tgc Cys	cag Gln 160	acc Thr	tac Tyr		537
											agc Ser						585
											aaa Lys 190						633
											tat Tyr						681
							_				gta Val		-				729
											aca Thr						777
											ttc Phe						825
											aca Thr						873

260 265 270

	260					265					270					
	gac Asp															921
aac Asn	gta Val	aca Thr	aga Arg	tat Tyr 295	gcg Ala	gtg Val	gcc Ala	gtc Val	ctg Leu 300	ggc	tac Tyr	tac Tyr	aac Asn	cgc Arg 305	agg Arg	969
gjà aaa	atc Ile	aat Asn	cca Pro 310	gaa Glu	act Thr	ttt Phe	cta Leu	aat Asn 315	gaa Glu	atc Ile	aaa Lys	taç Tyr	atc Ile 320	gcc Ala	agt Ser	1017
gac Asp	cct Pro	gat Asp 325	gac Asp	aag Lys	cac His	ttc Phe	ttc Phe 330	aat Asn	gtc Val	act Thr	gat Asp	gag Glu 335	gct Ala	gcc Ala	ttg Leu	1065
_	gac Asp 340		-	_	_	_		-	-			_	_	_		1113
	aac Asn															1161
	tcc Ser															1209
	tat Tyr															1257
-	att Ile			_				_								1305
_	aac Asn 420			_		_				_		_	_			1353
	agg Arg															1401
_	ggc Gly	_	_		_								-			1449
	cac His	_	_	_			_	_							_	1497
gaa Glu	atc Ile	acc Thr 485	tcg Ser	gtg Val	gac Asp	atc Ile	gac Asp 490	ggc Gly	gac Asp	ggc Gly	gtg Val	act Thr 495	gat Asp	gtc Val	ctg Leu	1545
	gtg Val 500															1593
	tac Tyr	-			_	_	_				_				_	1641

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cta aag gat Leu Lys Asp	tca cac agt Ser His Ser 535	tac cag Tyr Gln	aat gcc Asn Ala 540	cga ttt ggg Arg Phe Gly	tcc tcc att 16 Ser Ser Ile 545	89
gcc tca gtt Ala Ser Val	cga gac cto Arg Asp Let 550	aac cag Asn Gln	gat tcc Asp Ser 555	tac aat gac Tyr Asn Asp	gtg gtg gtg 17 Val Val Val 560	37
gga gcc ccc Gly Ala Pro 565	ctg gag gad Leu Glu Asp	aac cac Asn His 570	gca gga Ala Gly	gcc atc tac Ala Ile Tyr 575	atc ttc cac 17 Ile Phe His	85
ggc ttc cga Gly Phe Arg 580	ggc agc ato Gly Ser Ile	ctg aag Leu Lys 585	aca cct Thr Pro	aag cag aga Lys Gln Arg 590	atc aca gcc 18 Ile Thr Ala	133
tca gag ctg Ser Glu Leu 595	gct acc ggc Ala Thr Gly 600	Leu Gln	tat ttt Tyr Phe	ggc tgc agc Gly Cys Ser 605	atc cac ggg 18 Ile His Gly 610	81
caa ttg gac Gln Leu Asp	ctc aat gag Leu Asn Gla 615	gat ggg 1 Asp Gly	ctc atc Leu Ile 620	gac ctg gca Asp Leu Ala	gtg gga gcc 19 Val Gly Ala 625	29
ctt ggc aac Leu Gly Asn	gct gtg at Ala Val Il 630	ctg tgg Leu Trp	tcc cgc Ser Arg 635	cca gtg gtt Pro Val Val	cag atc aat 19 Gln Ile Asn 640	977
gcc agc ctc Ala Ser Leu 645	cac ttt ga His Phe Gl	g cca tcc ı Pro Ser 650	aag atc Lys Ile	aac atc ttc Asn Ile Phe 655	cac aga gac 20 His Arg Asp	25
tgc aag cgc Cys Lys Arg 660	agt ggc ag Ser Gly Ar	g gat gcc g Asp Ala 665	acc tgc Thr Cys	ctg gcc gcc Leu Ala Ala 670	ttc ctc tgc 20 Phe Leu Cys	73
ttc acg ccc Phe Thr Pro 675	atc ttc ct Ile Phe Le 68	u Ala Pro	cat ttc His Phe	caa aca aca Gln Thr Thr 685	act gtt ggc 21 Thr Val Gly 690	121
atc aga tac Ile Arg Tyr	aac gcc ac Asn Ala Th 695	c atg gat r Met Asp	gag agg Glu Arg 700	Arg Tyr Thr	ccg agg gcc 21 Pro Arg Ala 705	169
cac ctg gac His Leu Asp	gag ggc gg Glu Gly Gl 710	g gac cga y Asp Arg	ttc acc Phe Thr 715	aac aga gcc Asn Arg Ala	gta ctg ctc 22 Val Leu Leu 720	217
tcc tcc ggc Ser Ser Gly 725	Gln Glu Le	c tgt gag u Cys Glu 730	Arg Ile	aac ttc cat Asn Phe His 735	Val Leu Asp	265
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gag gac cct Glu Asp Pro 755	gac cat gg Asp His Gl 76	y Pro Met	ctg gad Leu Asp	gac ggc tgg Asp Gly Trp 765	Pro Thr Thr 770	361
ctc aga gtc Leu Arg Val	tcg gtg co Ser Val Pr	c ttc tgg o Phe Trp	aac ggc Asn Gly	tgc aat gag Cys Asn Glu	gat gag cac 20 Asp Glu His	409

WO 01/55437 PCT/US01/02623 775 780 tgt gtc cct qac ctt qtq ttg gat gcc cgg agt qac ctq ccc acq gcc 2457 Cys Val Pro Asp Leu Val Leu Asp Ala Arg Ser Asp Leu Pro Thr Ala 795 790 atg gag tac tgc cag agg gtg ctg agg aag cct gcg cag gac tgc tcc 2505 Met Glu Tyr Cys Gln Arg Val Leu Arg Lys Pro Ala Gln Asp Cys Ser 805 810 gca tac acg ctg tcc ttc gac acc aca gtc ttc atc ata gag agc aca 2553 Ala Tyr Thr Leu Ser Phe Asp Thr Thr Val Phe Ile Ile Glu Ser Thr 825 820 ege cag ega gtg geg gtg gag gee aca etg gag aac agg gge gag aac 2601 Arg Gln Arg Val Ala Val Glu Ala Thr Leu Glu Asn Arg Gly Glu Asn 835 **B40** 845 gcc tac agc acg gtc cta aat atc tcg cag tca qca aac ctg cag ttt 2649 Ala Tyr Ser Thr Val Leu Asn Ile Ser Gln Ser Ala Asn Leu Gln Phe 855 ged agd ttg atd dag gag gad tda gad ggt agd att gag tgt gtg 2697 Ala Ser Leu Ile Gln Lys Glu Asp Ser Asp Gly Ser Ile Glu Cys Val 875 870 aac gag. gag agg agg ctc cag aag caa gtc tgc aac gtc agc tat ccc 2745 Asn Glu Glu Arg Arg Leu Gln Lys Gln Val Cys Asn Val Ser Tyr Pro 890 ttc ttc cgg gcc aag gcc aag gtg gct ttc cgt ctt gat ttt gag ttc 2793 Phe Phe Arg Ala Lys Ala Lys Val Ala Phe Arg Leu Asp Phe Glu Phe 905 age aaa tee ate tte eta cae cae etg gag ate gag ete get gea gge 2841 Ser Lys Ser Ile Phe Leu His His Leu Glu Ile Glu Leu Ala Ala Gly 920 925 agt gac agt aat gag cgg gac agc acc aag gaa gac aac gtg gcc ccc 2889 Ser Asp Ser Asn Glu Arg Asp Ser Thr Lys Glu Asp Asn Val Ala Pro 935 940 tta cgc ttc cac ctc aaa tac gag gct gac gtc ctc ttc acc agg agc 2937 Leu Arg Phe His Leu Lys Tyr Glu Ala Asp Val Leu Phe Thr Arg Ser 950 955 age age etg age cae tat gag gte aag eee aac age teg etg gag aga 2985 Ser Ser Leu Ser His Tyr Glu Val Lys Pro Asn Ser Ser Leu Glu Arg 965 tac gat ggt atc ggg cct ccc ttc agc tgc atc ttc agg atc cag aac 3033 Tyr Asp Gly Ile Gly Pro Pro Phe Ser Cys Ile Phe Arg Ile Gln Asn 985 ttg ggc ttg ttc ccc atc cac ggg atg atg atg aag atc acc att ccc 3081 Leu Gly Leu Phe Pro Ile His Gly Met Met Lys Ile Thr Ile Pro

3129

3177

atc gcc acc agg agc ggc aac cgc cta ctg aag ctg agg gac ttc ctc

Ile Ala Thr Arg Ser Gly Asn Arg Leu Leu Lys Leu Arg Asp Phe Leu

acg gac gag gcg aac acg tcc tgt aac atc tgg ggc aat agc act gag

Thr Asp Glu Ala Asn Thr Ser Cys Asn Ile Trp Gly Asn Ser Thr Glu

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WO 01/55437	PCT/US01/02623
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aat cac agc aac tct gat gtc gtc tcc atc aac tgc aat ata cg Asn His Ser Asn Ser Asp Val Val Ser Ile Asn Cys Asn Ile Ar 1060 1065 1070	
gtc ccc aac cag gaa atc aat ttc cat cta ctg ggg aac ctg tg Val Pro Asn Gln Glu Ile Asn Phe His Leu Leu Gly Asn Leu Tr 1075 1080 1085	
agg tcc cta aaa gca ctc aag tac aaa tcc atg aaa atc atg gt Arg Ser Leu Lys Ala Leu Lys Tyr Lys Ser Met Lys Ile Met Va 1095 1100 110	l Asn
gca gcc ttg cag agg cag ttc cac agc ccc ttc atc ttc cgt gag Ala Ala Leu Gln Arg Gln Phe His Ser Pro Phe Ile Phe Arg Gl 1110 1115 1120	g gag 3417 u Glu
gat ccc agc cgc cag atc gtg ttt gag atc tcc aag caa gag ga Asp Pro Ser Arg Gln Ile Val Phe Glu Ile Ser Lys Gln Glu As 1125 1130 1135	
cag gtc ccc atc tgg atc att gta ggc agc acc ctg ggg ggc ct Gln Val Pro Ile Trp Ile Ile Val Gly Ser Thr Leu Gly Gly Le 1140 1145 1150	c cta 3513 u Leu
ctg ctg gcc ctg ctg gtc ctg gca ctg tgg aag ctc ggc ttc tt Leu Leu Ala Leu Leu Val Leu Ala Leu Trp Lys Leu Gly Phe Ph 1155 1160 1165	
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agetggtttt aagtggaact geectactgg gagactggga cacetttaac aca	gacccct 3845
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<211> 735

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<213> Homo sapiens

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Phe Pro Leu Trp Lys Leu Leu Asn Val Leu Val Cys Ile Phe Ser Ser

5

10

15

56

ttc atc atg ctg aat att tac tgt acc ctt ttg atc tgg aaa ttt att

Phe Ile Met Leu Asn Ile Tyr Cys Thr Leu Leu Ile Trp Lys Phe Ile

20 35 35

tat tca gct ttt ttc tgt tat att act tct ttg atg att ttc ccc ttt

Tyr Ser Ala Phe Phe Cys Tyr Ile Thr Ser Leu Met Ile Phe Pro Phe

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40 45 50	
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atc ttc ttc ctt tat ctg tac tcc tca aga taa atgctaga agttggttaa 2 Ile Phe Phe Leu Tyr Leu Tyr Ser Ser Arg * 70 75	29
gccaggactt aaacccagct tgtagcttta taagctgggt tttgaacctc agttttctag 3	35:
ttagtaaagt gatcatgaga ataacgacct caaaggatat catgaggatt aaattagatt 4	11:
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tgctgtcatg ttcactatta atttatttaa caaatattta ttgaatgcta atacaaatgt 5	539
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tct atc ttg gtg tgt aca gaa ttg gga ctt ggc agg ttg acc ttc cct Ser Ile Leu Val Cys Thr Glu Leu Gly Leu Gly Arg Leu Thr Phe Pro 10 15 20 25	21
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gtc ttg gag gct tgg gtc tgg taa ataattgagc ctgagctcac aatcctgccc 3: Val Leu Glu Ala Trp Val Trp * 45	23
ctgggtccag gtggctggtc tgctgccccc aaaagcctga ccttcttggt cctgtgggtc 3	83

443

503

563

623

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agtaccgccc tgggtagctc aattaacgaa ttttcaagac ccaggccttg gcgctccttg

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115

aca gct tgg gag gct aat ctg cca aag ggg agg cat act cac cct gaa

Thr Ala Trp Glu Ala Asn Leu Pro Lys Gly Arg His Thr His Pro Glu

100

686

95

tgt cta gct cct ctt ctt gtc cct tgt aaa tgt gca ttt cca ctt tac
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125 130 135

tgattatatt ct 734

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Met Ala Trp Ile Pro Leu Phe Leu Gly Val

1 5 10

ctt gct tac tgc aca gga tcc gtg gcc tcc tat gag ctg act cag cca
Leu Ala Tyr Cys Thr Gly Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro

20
25

ccc tca gtg tcc gtg tcc cca gga cag aca gcc agc atc acc tgc tct
Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser
30 35 40

gga gat aaa ttg ggg gat aaa tat gct tgc tgg tat cag cag aag cca 254
Gly Asp Lys Leu Gly Asp Lys Tyr Ala Cys Trp Tyr Gln Gln Lys Pro
45 50 55

ggc cag tcc cct gtg ctg gtc atc tat caa gat agc aag cgg ccc tca

Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser

60 65 70

ggg atc cct gag cga ttc tct ggc tcc aac tct ggg aac aca gcc act
Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr
75 80 85 90

ctg acc atc agc ggg acc cag gct atg gat gag gct gac tat tac tgt

198

Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys

100

105

cag gcg tgg gac agc act ctt tat gtc ttc gga act ggg acc aag
Gln Ala Trp Asp Ser Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Lys
110 115 120

gtc acc gtc cta ggt cag ccc aag gcc aac ccc act gtc act ctg ttc 494
Val Thr Val Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe
125 130 135

ccg ccc tcc tct gag gag ctc caa gcc aac aag gcc aca cta gtg tgt
Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys
140
145
150

ctg atc agt gac ttc tac ccg gga gct gtg aca gtg gcc tgg aag gca
Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala
155 160 165 170

Asp Gly Ser Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys 175 180 185	638
cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro 190 195 200	686
gag cag tgg aag tcc cac aga agc tac agc tgc cag gtc acg cat gaa Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu 205 210 215	734
ggg agc acc gtg gag aag aca gtg gcc cct aca gaa tgt tca tag gtt Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser * 220 225 230	782
ctaaaccctc acctcccccc acgggagact agagctgcag gatcccaggg gaggggtctc	842
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atgccaaagt ctatgtggct aaagtggact gcacggccca ctccgacgtg tgctccgccc  agggggtgcg aggatacccc accttaaagc ttttcaagcc aggccaagaa gctgtgaagt  accagggtcc tcgggacttc cagacactgg aaaactgg atg ctg cag aca ctg Met Leu Gln Thr Leu 1 5  aac gag gag cca gtg aca cca gag ccg gaa gtg gaa ccg ccc agt gcc Asn Glu Glu Pro Val Thr Pro Glu Pro Glu Val Glu Pro Pro Ser Ala 10 15 20  ccc gag ctc aag caa ggg ctg tat gag ctc tca gca agc aac ttt gag Pro Glu Leu Lys Gln Gly Leu Tyr Glu Leu Ser Ala Ser Asn Phe Glu	120 180 233 281
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ctt ctc t Leu Leu 1	rrp Pi	tc cga he Arg 05	gat Asp	Gly 333	aaa Lys	aag Lys 110	gtg Val	gat Asp	cag Gln	tac Tyr	aag Lys 115	gga Gly	aag Lys	569
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aca gag a Thr Glu 1	act go Thr G	ga gcg ly Ala	acg Thr	gag Glu 140	acc Thr	gtc Val	acg Thr	ccc Pro	tca Ser 145	gag Glu	gcc Ala	ccg Pro	gtg Val	665
ctg gca g Leu Ala i 150	get ga Ala G	ag ccc lu Pro	gag Glu 155	gct Ala	gac Asp	aag Lys	ggc Gly	act Thr 160	gtg Val	ttg Leu	gca Ala	ctc Leu	act Thr 165	713
gaa aat a Glu Asn a	aac t Asn P	tc gat he Asp 170	gac Asp	acc Thr	att Ile	gca Ala	gaa Glu 175	gga Gly	ata Ile	acc Thr	ttc Phe	atc Ile 180	aag Lys	761
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<sup>&</sup>lt;210> 109

<sup>&</sup>lt;211> 1471

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

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wo	01/55	5437												ı	CT/USU	1/02623
Ala T	Thr	Phe	Trp	Gln 220	Asn	Pro	Arg	Asn	His 225	Phe	Arg	Cys	Gln	Val 230	Gln	
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cct g Pro V	/al															880
ggc t Gly E																928
ctc t Leu 1 280																976
agt g Ser A	_			_	_	-	_	_	_	-	_	_		_		1024
tagct	tcca	aa a	accai	tecea	ag gt	catt	ctto	c ato	cctca	accc	agga	attcı	cc 1	tgtad	ectget	1084
cccaa	atct	gt	gttc	ctaaa	aa gt	gatt	ctca	cto	etget	tct	cato	etect	ac 1	ttaca	atgaat	1144
actto	ctct	ct t	tttt	tctg	tt to	cccts	gaaga	a ttg	gaget	ccc	aaco	ccca	aag 1	tacga	aatag	1204
gctaa	aacc	aa t	taaaa	aaati	tg to	gtgtt	ggg	ctg	ggttg	gcat	ttca	aggag	gtg 1	tctg	ggagt	1264
tctg	ctca	itc a	actg	accta	at c	tate	gatti	t agg	ggaaa	agca	gcat	tec	ett (	ggac	atctga	1324
agtga	acag	icc (	ctcti	ttct	et co	cacco	caato	g cto	gctti	cctc	ctgt	tcat	ccc 1	tgate	ggaagt	1384
cctca	aaac	ac o	catt	tccat	ta co	ccago	gcatt	t cts	gggto	ccc	acto	ggagg	ggt 1	tagto	ctgaag	1444
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30 . 35 40

		50					33					••				
														gtc Val		255
tgg Trp 60	ttc Phe	cgg Arg	gac Asp	Gly aaa	gag Glu 65	atc Ile	cca Pro	tac Tyr	tac Tyr	gct Ala 70	gag Glu	gtt Val	gtg Val	gcc Ala	aca Thr 75	303
aac Asn	aac Asn	cca Pro	gac Asp	aga Arg 80	aga Arg	gtg Val	aag Lys	cca Pro	gag Glu 85	acc Thr	cag Gln	ggc Gly	cga Arg	ttc Phe 90	cgc Arg	351
														gga Gly		399
_	_	_		_	_		_				-			aga Arg		447
	-	-			_			-		-	_		_	gag Glu		495
	_	_					-				_			ctg Leu		543
														tgt Cys 1'70		591
														agc Ser		639
_	-					_		-						ccc Pro		687
		-							_	~	-		-	caa Gln		735
														tat Tyr		783
	_										_			atc Ile 250	-	831
														cgg Arg		879
	_	_	_		-				_		_	_		ttc Phe	_	927
			-	_		_								atc Ile	_	975

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_	_		-	_			_				Leu				_	
				320	_				325					330		

Glu Leu Arg Arg Val Arg Ser Ala Glu Glu Gly Gly Phe Thr Cys Arg

tac	tcc	ctc	cca	cag	ttg	ctg	ggc	CCC	tcc	tgc	tcc	tgg	gag	gct	gag	1119
Tyr	Ser	Leu	Pro	Gln	Leu	Leu	Gly	Pro	Ser	Cys	Ser	Trp	Glu	Ala	Glu	
_			225					340					345			

atg	gat	gat	gaa	gac	ccc	att	atg	ggt	acc	atc	acc	tcg	ggt	tcc	agg	1551
Met	Asp	Asp	Glu	Asp	Pro	Ile	Met	Gly	Thr	Ile	Thr	Ser	Gly	Ser	Arg	
				480					485					490		

aag Lys																1599
цуs	uys	FIU	TTD	FLO	nap	Der	PLO	GTÅ	ASP	GIII	Ara	Ser	Pro	Pro	GIY	
			495					500					ENE			

gat	gcc	cct	CCC	ttg	gaa	gaa	caa	aag	gag	ctc	cat	tat	gcc	tcc	ctt	1647
															Leu	
		510					515					520				

agt Ser	ttt Phe	tct Ser	gag Glu	atg Met	aag Lys	tcg Ser	agg Arg	gag Glu	cct Pro	aag Lys	gac Asp	cag Gln	gag Glu	gcc Ala	cca Pro	1695
	525					530				•	535					

agc	acc	acg	gag	tac	tcg	gag	atc	aag	aca	agc	aag	tga	ggatttgccc	174	44
Ser	Thr	Thr	Glu	Tvr	Ser	Glu	Tle	Lvs	Thr	Ser	Laze	*			

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545 540 550

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WC	) 01/5	5437												j	PC 1/U	501/02023
Ile	Leu	Phe	Thr	His 115	Gly	Lys	Pro	Gln	Glu 120	Arg	Lys	Asp	Ala	Arg 125	Ser	
cag Gln	aag Lys	aat Asn	aca Thr 130	aaa Lys	gta Val	gac Asp	ttc Phe	ttt Phe 135	gcc Ala	gtg Val	gaa Glu	ctc Leu	ctc Leu 140	gat Asp	ggc Gly	973
						gac Asp										1021
gcc Ala	act Thr 160	cag Gln	aag Lys	aaa Lys	gcc Ala	aat Asn 165	gat Asp	GJÀ aaa	gaa Glu	tgg Trp	tac Tyr 170	cat His	gtg Val	gac Asp	att Ile	1069
						ggt Gly										1117
			-	_		gag Glu	_			-	_	_	-		_	1165
_		_			_	ccg Pro			_	_						1213
						atg Met										1261
						ggg Gly 245										1309
						ggt Gly										1357
_	_	_	_	_	_	tac Tyr		_	_			_		_		1405
						atc Ile										1453
						gag Glu										1501
_		_	-			atg Met 325		_	_	_				_		1549
-				-		atg Met		_		_			_	_		1597
					Asp	tct Ser	-	-		-	_	-		_	-	1645
ggg	<b>3</b> 99	cgt	gtc	aag	ctc	atg	gtt	aac	tta	gac	tgt	atc	agg	ata	aac	1693

WC	01/5	5437												1	PCT/US	801/02623
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					gga Gly											1741
aat Asn	gac Asp 400	aac Asn	gag Glu	tgg Trp	cac His	acc Thr 405	gtt Val	cgg Arg	gtg Val	gtg Val	cgg Arg 410	aga Arg	gga Gly	aaa Lys	agc . Ser	1789
ctt Leu 415	aag Lys	tta Leu	acc Thr	gtg Val	gat Asp 420	gat Asp	gat Asp	gtg Val	gct Ala	gag Glu 425	ggt Gly	aca Thr	atg Met	gtg Val	gga Gly 430	1837
gac Asp	cat His	acc Thr	cgt Arg	ttg Leu 435	gag Glu	ttc Phe	cac His	aac Asn	att Ile 440	gaa Glu	acg Thr	gga Gly	atc Ile	atg Met 445	act Thr	1885
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_	-		_		aat Asn						-					1981
ggt Gly	gac Asp 480	att Ile	gat Asp	tat Tyr	tgt Cys	gag Glu 485	ctg Leu	aag Lys	gct Ala	cgt Arg	ttt Phe 490	gga Gly	ctg Leu	agg Arg	aac Asn	2029
		-	_		gtc Val 500			_		_	_					2077
	_			_	gct Ala				_					_		2125
_					gat Asp							_		-		2173
	-				gtc Val			_	_			_				2221
	-				ggt Gly								_	-		2269
					cag Gln 580											2317
-				_	ctg Leu			-			_	_		_	-	2365
					aat Asn											2413
ggt	ctg	gcc	caa	ggc	atg	tac	agc	aac	ctc	cca	aag	ctc	gtg	gcc	tct	2461

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ctg Leu 655	cca Pro	gac Asp	ctc Leu	atc Ile	aat Asn 660	gat Asp	gct Ala	ctt Leu	cat His	cgg Arg 665	agc Ser	gga Gly	cag Gln	atc Ile	gag Glu 670	2557
cgt Arg	ggc Gly	tgt Cys	gaa Glu	gga Gly 675	ccc Pro	agt Ser	acc Thr	acc Thr	tgc Cys 680	cag Gln	gaa Glu	gat Asp	tca Ser	tgt Cys 685	gcc Ala	2605
aac Asn	cag Gln	gly aaa	gtc Val 690	tgc Cys	atg Met	caa Gln	caa Gln	tgg Trp 695	gag Glu	ggc Gly	ttc Phe	acc Thr	tgt Cys 700	gat Asp	tgt Cys	2653
tct Ser	atg Met	acc Thr 705	tct Ser	tat Tyr	tct Ser	gga Gly	aac Asn 710	cag Gln	tgc Cys	aat Asn	gat Asp	cct Pro 715	ggc Gly	gct Ala	acg Thr	2701
tac Tyr	atc Ile 720	ttt Phe	gly aaa	aaa Lys	agt Ser	ggt Gly 725	g1y ggg	ctt Leu	atc Ile	ctc Leu	tac Tyr 730	acc Thr	tgg Trp	cca Pro	gcc Ala	2749
aat Asn 735	gac Asp	agg Arg	ccc Pro	agc Ser	acg Thr 740	cgg Arg	tct Ser	gac Asp	cgc Arg	ctt Leu 745	gcc Ala	gtg Val	ggc Gly	ttc Phe	agc Ser 750	2797
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					cag Gln				Glu							2893
gtc Val	ttc Phe	aac Asn 785	Ile	ggc Gly	aca Thr	gtt Val	gac Asp 790	Ile	tcc Ser	atc Ile	aaa Lys	gag Glu 795	gag Glu	aga Arg	acc Thr	2941
cct Pro	gta Val 800	Asn	gac Asp	ggc	aaa Lys	tac Tyr 805	cat His	gtg Val	gta Val	cgc Arg	ttc Phe 810	Thr	agg Arg	aac Asn	ggc Gly	2989
	Asn				cag Gln 820	Val					Val					3037
					Leu					Thr						3085
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			Asp		_		_	Leu		_		_	Glu		aac Asn	3181
ccc	aat	att	aaa	ato	aat	gga	agt	gtt	cgg	ctg	gtt	gga	gaa	gto	cca	3229

WO 01/35457	,02020
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act act gtc atg gaa acc act act aca atg gcg act acc aca acc cgt Thr Thr Val Met Glu Thr Thr Thr Thr Met Ala Thr Thr Thr Thr Arg 915 920 925	3325
aag aat cgc tct aca gcc agc att cag cca aca tca gat gat ctt gtt Lys Asn Arg Ser Thr Ala Ser Ile Gln Pro Thr Ser Asp Asp Leu Val 930 935 940	3373
tca tct gct gaa tgt tca agt gat gat gaa gac ttt gtt gaa tgt gag Ser Ser Ala Glu Cys Ser Ser Asp Asp Glu Asp Phe Val Glu Cys Glu 945 950 955	3421
ccg agt aca gca aac ccc acg gag ccg gga atc aga cgg gtt ccg ggg Pro Ser Thr Ala Asn Pro Thr Glu Pro Gly Ile Arg Arg Val Pro Gly 960 965 970	3469
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acg cgg aac tac atc agc aac tcc gcc cag agc aac ggc acg ctc atg Thr Arg Asn Tyr Ile Ser Asn Ser Ala Gln Ser Asn Gly Thr Leu Met 1025 1030 1035	3661
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130 135 140

			130					133					140			
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cca Pro	ttc Phe	acc Thr	gcc Ala	agt Ser 195	Gly 999	gag Glu	agc Ser	gag Glu	atc Ile 200	ctg Leu	gac Asp	ctg Leu	gaa Glu	gga Gly 205	gac Asp	1165
atg Met	tac Tyr	ctg Leu	gga Gly 210	Gly 999	ctg Leu	ccg Pro	gag Glu	aac Asn 215	cgt Arg	gct Ala	ggc Gly	ctt Leu	att Ile 220	ctc Leu	ccc Pro	1213
acc Thr	gag Glu	ctg Leu 225	tgg Trp	act Thr	gcc Ala	atg Met	ctc Leu 230	aac Asn	tat Tyr	ggc Gly	tac Tyr	gtg Val 235	ggc Gly	tgc Cys	atc Ile	1261
ege Arg	gac Asp 240	cta Leu	ttc Phe	att Ile	gat Asp	999 Gly 245	cgc Arg	agc Ser	aag Lys	aac Asn	att Ile 250	cga Arg	cag Gln	ctg Leu	gca Ala	1309
gag Glu 255	atg Met	cag Gln	aat Asn	gct Ala	gcg Ala 260	ggt Gly	gtc Val	aag Lys	tcc Ser	tcc Ser 265	tgt Cys	tca Ser	cgg Arg	atg Met	agt Ser 270	1357
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gct Ala	acg Thr	acc Thr	tcc Ser	agg Arg 355	Asp	tct Ser	gcc	gac Asp	acc Thr 360		cgt Arg	ctg Leu	gag Glu	ctg Leu 365	Asp	1645
Gly	gly ggg	cgt Arg	gtc Val 370	Lys	ctc Leu	atg Met	gtt Val	aac Asn 375	Leu	gac Asp	tgt Cys	ato Ile	agg Arg 380	Ile	aac Asn	1693
tgt Cys	aac Asn	tco Ser	ago Ser	aaa Lys	gga Gly	cca Pro	gag Glu	acc Thr	ttg Leu	tat Tyr	gca Ala	Gly	cag Gln	aag Lys	ctc Leu	1741

385 390 395 .

		385					390					395				•
aat Asn	gac Asp 400	aac Asn	gag Glu	tgg Trp	cac His	acc Thr 405	gtt Val	cgg Arg	gtg Val	gtg Val	cgg Arg 410	aga Arg	gga Gly	aaa Lys	agc Ser	1789
ctt Leu 415	aag Lys	tta Leu	acc Thr	gtg Val	gat Asp 420	gat Asp	gat Asp	gtg Val	gct Ala	gag Glu 425	ggt Gly	aca Thr	atg Met	gtg Val	gga Gly 430	1837
gac Asp	cat His	acc Thr	cgt Arg	ttg Leu 435	gag Glu	ttc Phe	cac His	aac Asn	att Ile 440	gaa Glu	acg Thr	gga Gly	atc Ile	atg Met 445	act Thr	1885
Glu	aaa Lys	Arg	Tyr 450	Ile	Ser	Val	Val	Pro 455	Ser	Ser	Phe	Ile	Gly 460	His	Leu	1933
Gln	agc Ser	Leu 465	Met	Phe	Asn	Gly	Leu 470	Leu	Tyr	Ile	Asp	Leu 475	Cys	Lys	Asn	1981
Gly	gac Asp 480	Ile	Asp	Tyr	Суѕ	Glu 485	Leu	Lys	Ala	Arg	Phe 490	Gly	Leu	Arg	Asn	2029
Ile 495		Ala	Asp	Pro	Val 500	Thr	Phe	Lys	Thr	Lys 505	Ser	Ser	Tyr	Leu	Ser 510	2077
Leu	gcc Ala	Thr	Leu	Gln <b>51</b> 5	Ala	Tyr	Thr	Ser	Met 520	His	Leu	Phe	Phe	Gln 525	Phe	2125
aag Lys	acc Thr	acc Thr	tca Ser 530	Pro	gat Asp	ggc	ttc Phe	att Ile 535	Leu	ttc Phe	aat Asn	agt Ser	ggt Gly 540	Asp	ggc	2173
aat Asr	gac n Asp	tto Phe 545	lle	gca Ala	gtc Val	gag Glu	Ctt Leu 550	Val	aag Lys	Gly 999	tat Tyr	ata Ile 555	His	tac Tyr	gtt Val	2221
ttt Phe	gac Asp 560	Let	gga Gly	aac Asn	ggt Gly	Pro 565	Asn	gtg Val	ato Ile	aaa Lys	ggd Gly 570	Asn	agt Ser	gac Asp	cgc Arg	2269
Pro 57	o Leu	g aat 1 Asr	gac n Asp	aac Asr	cag Gln 580	Trp	cac His	aat Asn	gto Val	gto Val 585	. Ile	act Thr	cgg	gac Asp	aat Asn 590	2317
agi Se:	t aad r Asr	e act	cat His	ago Ser 595	: Leu	aaa Lys	gtg Val	g gad L Asp	t acc	: Lys	gtg Val	gto Val	act Thr	Glr G05	gtt Val	2365
ate Ile	c aat e Ası	ggt Gly	gco Ala 610	Lys	a aat s Asn	: ctg ı Lev	gat 1 Asp	ttg Lev 615	ı Lys	ggt Gl	gat Asp	t cto	tat Tyr 620	Met	gct Ala	2413
gg gg	t cto y Le	g gco 1 Ala 62	a Glr	a ggo a Gly	ato Met	tac Tyr	ago Sei 630	c Asr	cto Le	c cca	a aag o Lys	g cto Let 635	ı Val	g gco L Ala	tct a Ser	2461
cg.	a gat g As	gg Gl	c ttt y Phe	caq e Gl	g ggo n Gly	tgt Cys	cta Lei	a gca ı Ala	a tca a Sei	a ggg	g gad Y Asp	tto Lei	g aat ı Ası	gga Gly	a cgc / Arg	2509

640 645 650

ctg Leu 655	cca Pro	gac Asp	ctc Leu	atc Ile	aat Asn 660	gat Asp	gct Ala	ctt Leu	cat His	cgg Arg 665	agc Ser	gga Gly	cag Gln	atc Ile	gag Glu 670	2557
cgt Arg	ggc Gly	tgt Cys	gaa Glu	gga Gly 675	ccc Pro	agt Ser	acc Thr	acc Thr	tgc Cys 680	cag Gln	gaa Glu	gat Asp	tca Ser	tgt Cys 685	gcc Ala	2605
aac Asn	cag Gln	gly aaa	gtc Val 690	tgc Cys	atg Met	caa Gln	caa Gln	tgg Trp 695	gag Glu	ggc Gly	ttc Phe	acc Thr	tgt Cys 700	gat Asp	tgt Cys	2653
tct Ser	atg Met	acc Thr 705	tct Ser	tat Tyr	tct Ser	gga Gly	aac Asn 710	cag Gln	tgc Cys	aat Asn	gat Asp	cct Pro 715	ggc Gly	gct Ala	acg Thr	2701
tac Tyr	atc Ile 720	ttt Phe	gjå aaa	aaa Lys	agt Ser	ggt Gly 725	Gly 999	ctt Leu	atc Ile	ctc Leu	tac Tyr 730	acc Thr	tgg Trp	cca Pro	gcc Ala	2749
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acc Thr	act Thr	gtg Val	aag Lys	gat Asp 755	ggc Gly	atc Ile	ttg Leu	gtc Val	cgc Arg 760	atc Ile	gac Asp	agt Ser	gct Ala	cca Pro 765	gga Gly	2845
ctt Leu	ggt Gly	gac Asp	ttc Phe 770	ctc Leu	cag Gln	ctt Leu	cac His	ata Ile 775	gaa Glu	cag Gln	Gly ggg	aaa Lys	att Ile 780	gga Gly	gtt Val	2893
gtc Val	ttc Phe	aac Asn 785	att Ile	ggc Gly	aca Thr	gtt Val	gac Asp 790	atc Ile	tcc Ser	atc Ile	aaa Lys	gag Glu 795	gag Glu	aga Arg	acc Thr	2941
cct Pro	gta Val 800	aat Asn	gac Asp	ggc	aaa Lys	tac Tyr 805	cat His	gtg Val	gta Val	cgc Arg	ttc Phe 810	acc Thr	agg Arg	aac Asn	ggc Gly	2989
ggc Gly 815	aac Asn	gcc Ala	acc Thr	ctg Leu	cag Gln 820	gtg Val	gac Asp	aac Asn	tgg Trp	cca Pro 825	gtg Val	aat Asn	gaa Glu	cat His	tat Tyr 830	3037
cct Pro	aca Thr	ggc	aac Asn	act Thr 835	gat Asp	aat Asn	gaa Glu	cgc Arg	ttc Phe 840	caa Gln	atg Met	gta Val	aaa Lys	cag Gln 845	aaa Lys	3085
			aaa Lys 850													3133
ggc Gly	cgg Arg	cag Gln 865	tta Leu	acc Thr	atc Ile	ttc Phe	aac Asn 870	act Thr	cag Gln	gcg Ala	caa Gln	ata Ile 875	gcc Ala	att Ile	ggt Gly	3181
		Asp	aaa Lys													3229
tat Tyr	gat Asp	ggt Gly	ttg Leu	aaa Lys	gta Val	ctg Leu	aac Asn	atg Met	gcg Ala	gct Ala	gag Glu	aac Asn	aac Asn	ccc Pro	aat Asn	3277

WO 01/55437 PCT/US01/0	2623
895 900 905 910	
att aaa atc aat gga agt gtt cgg ctg gtt gga gaa gtc cca tca att Ile Lys Ile Asn Gly Ser Val Arg Leu Val Gly Glu Val Pro Ser Ile 915 920 925	3325
ttg gga aca aca cag acg acc tcc atg cca cca gaa atg tct act act Leu Gly Thr Thr Gln Thr Thr Ser Met Pro Pro Glu Met Ser Thr Thr 930 935 940	3373
gtc atg gaa acc act act aca atg gcg act acc aca acc cgt aag aat Val Met Glu Thr Thr Thr Met Ala Thr Thr Thr Arg Lys Asn 945 950 955	3421
cgc tct aca gcc agc att cag cca aca tca gat gat ctt gtt tca tct Arg Ser Thr Ala Ser Ile Gln Pro Thr Ser Asp Asp Leu Val Ser Ser 960 965 970	3469
gct gaa tgt tca agt gat gat gaa gac ttt gtt gaa tgt gag ccg agt Ala Glu Cys Ser Ser Asp Asp Glu Asp Phe Val Glu Cys Glu Pro Ser 975 980 985 990	3517
aca gca aac ccc acg gag ccg gga atc aga cgg gtt ccg ggg gcc tca Thr Ala Asn Pro Thr Glu Pro Gly Ile Arg Arg Val Pro Gly Ala Ser 995 1000 1005	3565
gag gtg atc cgg gag tcg agc agc aca aca ggg atg gtc gtc ggc att Glu Val Ile Arg Glu Ser Ser Ser Thr Thr Gly Met Val Val Gly Ile 1010 1015 1020	3613
gtg gct gct gcc gcc ctc tgc atc ttg atc ctc ctg tac gcc atg tac Val Ala Ala Ala Leu Cys Ile Leu Ile Leu Leu Tyr Ala Met Tyr 1025 1030 1035	3661
aag tac agg aac agg gac gag ggg tcc tat caa gtg gac gag acg cgg Lys Tyr Arg Asn Arg Asp Glu Gly Ser Tyr Gln Val Asp Glu Thr Arg 1040 1045 1050	3709
aac tac atc agc aac tcc gcc cag agc aac ggc acg ctc atg aag gag Asn Tyr Ile Ser Asn Ser Ala Gln Ser Asn Gly Thr Leu Met Lys Glu 1055 1060 . 1065 1070	3757
aag cag cag agc tcg aag agc ggc cac aag aaa cag aaa aac aag gac Lys Gln Gln Ser Ser Lys Ser Gly His Lys Lys Gln Lys Asn Lys Asp 1075 1080 1085	3805
agg gag tat tac gtg taa acatge gaacaetget cacaegegag ttttcacagt Arg Glu Tyr Tyr Val  * 1090	3859
tatttctatc cacgcctatg aatctttgga cggtgagatc tcacagatgt cagaactgct	3919
ggaactatga aatggggtat ataaccacga ctctggtggg gaaaaccgtt ttttaaagga	3979
cacacacaca cacagogatg catotototo taaagotoag coacggotgo ggcaaggtoo	4039
cagcggtcgc tgggagacag aaggttttgt gccctgctgt atcataaagc acacacttag	4099 4159
egetetggag eeggaeggtg geteeaceae tteegeagge etagaaaett eetteteegg aggaeetttt actaaaaggt agaagaette atggettaet tgtteeataa eteeaagtga	4219
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acaaaactac aacaac 4295

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<213> Homo sapiens

<220> <221> CDS <222> (118)..(1494)

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gtg Val	gtc Val	ggt Gly	gcc Ala 20	tcc Ser	acg Thr	cca Pro	ggc	acc Thr 25	gtg Val	gtc Val	cga Arg	ctc Leu	aac Asn 30	aag Lys	gca Ala	213
gca Ala	ttg Leu	agc Ser 35	tac Tyr	gtg Val	tct Ser	gaa Glu	att Ile 40	gjå aaa	aaa Lys	gcc Ala	cct Pro	ctc Leu 45	cag Gln	cgg Arg	gcc Ala	261
ctg Leu	cag Gln 50	gtc Val	act Thr	gtc Val	cct Pro	cat His 55	ttc Phe	ctg Leu	gac Asp	tgg Trp	agt Ser 60	gga Gly	gag Glu	gcg Ala	ctt Leu	309
cag Gln 65	ccc Pro	acc Thr	agg Arg	atc Ile	cgg Arg 70	att Ile	ctg Leu	aat Asn	gtc Val	cat His 75	gtg Val	ccc Pro	cgc Arg	ctc Leu	cac His 80	357
ctg Leu	aaa Lys	ttc Phe	att Ile	gct Ala 85	ggt Gly	ttc Phe	gga Gly	gtg Val	cgc Arg 90	ctg Leu	ctg Leu	gca Ala	gca Ala	gct Ala 95	aat Asn	405
ttt Phe	act Thr	ttc Phe	aag Lys 100	Val	ttt Phe	cgc Arg	gcc Ala	cca Pro 105	gag Glu	ccc Pro	ctg Leu	gag Glu	ctg Leu 110	acg Thr	ctg Leu	453
cct Pro	gtg Val	gaa Glu 115	Leu	ctg Leu	gct Ala	gac Asp	acc Thr 120	Arg	gtg Val	acc Thr	cag Gln	agc Ser 125	Ser	atc Ile	agg Arg	501
acc Thr	cct Pro 130	Val	gtc Val	agc Ser	atc Ile	tct Ser 135	gcc Ala	tgc Cys	tct Ser	tta Leu	ttc Phe 140	tcg Ser	ggc	cac His	gcc Ala	549
aac Asn 145	Glu	ttt Phe	gat Asp	ggc Gly	agt Ser 150	Asn	ago Ser	acc Thr	tcc Ser	cac His	Ala	ctg Leu	ctg Leu	gtc Val	Leu 160	597
gtg Val	g cag Gln	aag Lys	g cac His	att Ile 165	Lys	gct Ala	gto Val	ttg Leu	agt Ser 170	Asn	aag Lys	ctg Leu	tgo Cys	Leu 175	agc Ser	645
ato Ile	tcc Ser	aac Asr	c ctg 1 Leu 180	ı Val	cag Gln	ggt Gly	gto Val	aat Asn 185	Val	cac His	ctg Lev	ggc Gly	acc Thr	Lev	att Ile	693
GJ7 ggc	cto Lev	aac Asr 195	ı Pro	gtg Val	ggt Gly	cct Pro	gag Glu 200	ı Ser	cag Glr	ato lle	cgc Arg	tat Tyr 205	Ser	atg Met	gtc Val	741
agt Sei	gtg Val	Pro	e act	gto Val	acc Thr	agt Ser 219	: Asp	tac Tyr	att Ile	tco Ser	Lev 220	ı Glı	a gto ı Val	aat Asr	gct Ala	789
	l Leu					/ Lys					ı Pro				acc Thr 240	837
					Arg					r Glu					c acc a Thr	885
gt	g ggd	cto	c to	c cas	g cag	gctg	g tti	t gad	tct	t gc	gcto	cte	g ctg	gctg	g cag	933

PCT/US01/02623 WO 01/55437 Val Gly Leu Ser Gln Gln Leu Phe Asp Ser Ala Leu Leu Leu Gln 265 981 aag gcc ggt gcc ctc aac ctg gac atc aca ggg cag ctg agg tcg gat Lys Ala Gly Ala Leu Asn Leu Asp Ile Thr Gly Gln Leu Arg Ser Asp 280 1029 gac aac ctg ctg aac acc tct gct ctg ggc cgg ctc atc ccg gag gtg Asp Asn Leu Leu Asn Thr Ser Ala Leu Gly Arg Leu Ile Pro Glu Val 290 1077 gcc cgc cag ttt ccc gag ccc atg cct gtg gtg ctc aag gtg cgg ctg Ala Arg Gln Phe Pro Glu Pro Met Pro Val Val Leu Lys Val Arg Leu 305 310 ggt gcc aca cct gtg gcc atg ctc cac aca aac aac gcc acc ctg cgg 1125 Gly Ala Thr Pro Val Ala Met Leu His Thr Asn Asn Ala Thr Leu Arg 330 325 ctg cag ccc ttc gtg gag gtc ctg gcc aca gcc tcc aac tcg gct ttc 1173 Leu Gln Pro Phe Val Glu Val Leu Ala Thr Ala Ser Asn Ser Ala Phe 345 cag tee etc tee etg gat gtg gta gtg aac ttg aga etc cag etc 1221 Gln Ser Leu Phe Ser Leu Asp Val Val Val Asn Leu Arg Leu Gln Leu 360 1269 tct gtg tcc aag gtg aag ctt cag ggg acc acg tct gtg ctg ggg gat Ser Val Ser Lys Val Lys Leu Gln Gly Thr Thr Ser Val Leu Gly Asp 375 gtc cag ctc acg gtg gcc tcc tcc aac gtg ggc ttc att gat aca gat 1317 Val Gln Leu Thr Val Ala Ser Ser Asn Val Gly Phe Ile Asp Thr Asp 390 395 cag gtg cgc aca ctg atg ggc acc gtt ttt gag aag ccc ctg ctg gac 1365 Gln Val Arg Thr Leu Met Gly Thr Val Phe Glu Lys Pro Leu Leu Asp 405 1413 cat etc aat get etc ttg gec atg gga att gec etc eet ggt gtg gte His Leu Asn Ala Leu Leu Ala Met Gly Ile Ala Leu Pro Gly Val Val 420 1461 aac etc cae tat gtt gee eet gag ate ttt gte tat gag gge tae gtg Asn Leu His Tyr Val Ala Pro Glu Ile Phe Val Tyr Glu Gly Tyr Val 440 gtg ata tcc agt gga ctc ttc tac cag agc tga ggcaagac cactgggagg 1512 Val Ile Ser Ser Gly Leu Phe Tyr Gln Ser \* 450 455 cctgagagtg ggccagctcg ctgctcaggc gaatttctca tttcaagcca ctggggaaac 1572 tgaggcaaaa ccatacttag tcatcaccaa caagctggac tgcttagctg ggctgtttta 1632 tettecetga gtgcctgggt etecetecet caettetgee etttecette etecteetet 1692 totoctccct cttccctcat ctcccccctc cttcctctgc cccaccccag gggggagcag 1752 actgetecte caggetgtat agacetgece tettgeatta aacaaettet ettgagetge 1812 aaaaaaaaa 1822

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gatatggctg gaaggacata gagtaaatga teggtetggt teategetaa aggagaetta	180
ggaacctag atg aag ttg gta ctt ctg aga aag aca tct ctt tct gtt Met Lys Leu Val Leu Leu Arg Lys Thr Ser Leu Ser Val 1 5 10	228
ttc act act cta ttc tca gta tcc agt tct cag tac cca gtt ctc agt Phe Thr Thr Leu Phe Ser Val Ser Ser Ser Gln Tyr Pro Val Leu Ser 15 20 25	276
acc tot att tgt aat act cot gta ttt agt act ttg ttt tta gtg toc Thr Ser Ile Cys Asn Thr Pro Val Phe Ser Thr Leu Phe Leu Val Ser 30 35 40 45	324
tgt tct gtt aac cct ctt cct agt acc gta ttt tta gta ctg cta tac Cys Ser Val Asn Pro Leu Pro Ser Thr Val Phe Leu Val Leu Leu Tyr 50 55 60	372
tca gtt gcc tgt ctg tag tacccc tgtacgtagt actcttttct tacaactctg Ser Val Ala Cys Leu * 65	426
ttcccagtac ccctatgttt agtcccttgt tctcatgttc tcactacccc aatacttaat	486
atactttgtt ctcagtatcc ttgttgttag taccctgttc tcactacccc ttttcttagt	546
acccctgagg ggggaaaaaa aggatgataa tggggtataa gtctcaaaaa acttttggat	606
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aggctggggg ccttgcgggg tgaggcaggg caagggtgtg agtcactgcc aggctgccaa	300
ageteactet geagetgtee agteecetgg ggtageecea ageetgteet tgtagggagt	360
ggcagccgga gtctgaactg tcctggggga ccaagcagga gcttaagatg ggcaagacct	420
ggggccctgg gcagacgcat caaagcaggc agaagcaggc atg gcc agc agg aag Met Ala Ser Arg Lys 1 5	475
acc aag aag gaa ggg ggt gcc ctc cgg gcc cag aga gcc tca tcc Thr Lys Lys Glu Gly Gly Ala Leu Arg Ala Gln Arg Ala Ser Ser 10 15 20	523
aat gtc ttc tcc aac ttt gag cag act cag atc cag gag ttc aag gag Asn Val Phe Ser Asn Phe Glu Gln Thr Gln Ile Gln Glu Phe Lys Glu 25 30 35	571
gca ttc aca ctc atg gat cag aac cga gat ggc ttc att gac aag gag Ala Phe Thr Leu Met Asp Gln Asn Arg Asp Gly Phe Ile Asp Lys Glu 40 45 50	619
gac ctg aag gac acc tat gcc tcc ctg ggc aag acc aac gtc aag gac Asp Leu Lys Asp Thr Tyr Ala Ser Leu Gly Lys Thr Asn Val Lys Asp 55 60 65	667
gac gag ctg gac gcc atg ctc aaa gag gcc tcg ggg ccc atc aac ttc Asp Glu Leu Asp Ala Met Leu Lys Glu Ala Ser Gly Pro Ile Asn Phe 70 75 80 85	715
acc atg ttt ctg aac ctg ttt ggg gag aag ctg agc ggt acc gac gcc Thr Met Phe Leu Asn Leu Phe Gly Glu Lys Leu Ser Gly Thr Asp Ala 90 95 100	763
gag gag acc att ctt aac gcc ttc aag atg ctg gac ccg gac ggg aaa Glu Glu Thr Ile Leu Asn Ala Phe Lys Met Leu Asp Pro Asp Gly Lys 105 110 115	811
ggg aaa atc aac aag gag tac atc aag cgt ctg ctg atg tcc cag gct Gly Lys Ile Asn Lys Glu Tyr Ile Lys Arg Leu Leu Met Ser Gln Ala 120 125 130	859
gac aag atg acg gcg gaa gag gtg gac cag atg ttc cag ttc gcc tcc Asp Lys Met Thr Ala Glu Glu Val Asp Gln Met Phe Gln Phe Ala Ser 135 140 145	907
atc gat gtg gcg ggc aac ctg gac tac aag gcg ctc agc tac gtg atc  Ile Asp Val Ala Gly Asn Leu Asp Tyr Lys Ala Leu Ser Tyr Val Ile  150 160 165	955
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gca gcc tcg gcc tcg ggt cag gcg gaa ggt aaa aag atc acc gat Ala Ala Ser Ala Ala Ser Gly Gln Ala Glu Gly Lys Lys Ile Thr Asp 10 15 20	160
ctg cgg gtc atc gat ctg aag tcc gag ctg aag cgg cgg aac tta gac Leu Arg Val Ile Asp Leu Lys Ser Glu Leu Lys Arg Arg Asn Leu Asp 25 30 35 40	208
atc acc gga gtc aag acc gtg ctc atc tcc cga ctc aag cag gct att Ile Thr Gly Val Lys Thr Val Leu Ile Ser Arg Leu Lys Gln Ala Ile 45 50 55	256
gaa gag gaa gga ggc gat cca gat aat att gaa tta act gtt tca act Glu Glu Glu Gly Gly Asp Pro Asp Asn Ile Glu Leu Thr Val Ser Thr 60 65 70	304
gat act cca aac aag aaa cca act aaa ggc aaa ggt aaa aaa cat gaa Asp Thr Pro Asn Lys Lys Pro Thr Lys Gly Lys Gly Lys Lys His Glu 75 80 85	352
gca gat gag ttg agt gga gat gct tct gtg gaa gat gat gct ttt atc Ala Asp Glu Leu Ser Gly Asp Ala Ser Val Glu Asp Asp Ala Phe Ile 90 95 100	400
aag gac tgt gaa ttg gag aat caa gag gca cat gag caa gat gga aat Lys Asp Cys Glu Leu Glu Asn Gln Glu Ala His Glu Gln Asp Gly Asn 105 110 115	448
gat gaa cta aag gac tct gaa gaa ttt ggt gaa aat gaa gaa aat Asp Glu Leu Lys Asp Ser Glu Glu Phe Gly Glu Asn Glu Glu Asn 125 130 135	496
gtg cat tcc aag gag tta ctc tct gca gaa gaa aac aag aga gct cat Val His Ser Lys Glu Leu Leu Ser Ala Glu Glu Asn Lys Arg Ala His 140 145 150	544
gaa tta ata gag gca gaa gga ata gaa gat ata gaa aaa gag gac atc Glu Leu Ile Glu Ala Glu Gly Ile Glu Asp Ile Glu Lys Glu Asp Ile 155 160 165	592
gaa agt cag gaa att gaa gct caa gaa ggt gaa gat gat acc ttt cta Glu Ser Gln Glu Ile Glu Ala Gln Glu Gly Glu Asp Asp Thr Phe Leu 170 175 180	640
aca gcc caa gat ggt gag gaa gaa gaa aat gag aaa gaa g	688
gct gag gct gat cac aca gct cat gaa gag atg gaa gct cat acg act Ala Glu Ala Asp His Thr Ala His Glu Glu Met Glu Ala His Thr Thr 205 210 215	736
gtg aaa gaa gct gag gat gac aac atc tcg gtc aca atc cag gct gaa Val Lys Glu Ala Glu Asp Asp Asn Ile Ser Val Thr Ile Gln Ala Glu 220 225 230	784
gat gcc atc act ctg gat ttt gat ggt gat gac ctc cta gaa aca ggt	832

PCT/US01/02623 WO 01/55437 Asp Ala Ile Thr Leu Asp Phe Asp Gly Asp Asp Leu Leu Glu Thr Gly 240 aaa aat gtg aaa att aca gat tgt gaa gca agt aag cca aaa gat ggg 880 Lys Asn Val Lys Ile Thr Asp Cys Glu Ala Ser Lys Pro Lys Asp Gly 255 250 cag ggc gcc att gca cag agg ccg gat aag gaa agc aag gat tat gag 928 Gln Gly Ala Ile Ala Gln Arg Pro Asp Lys Glu Ser Lys Asp Tyr Glu 275 265 270 atg aat gcg agc cat aaa gat ggt aag aag gaa gac tgc gtg aag ggt 976 Met Asn Ala Ser His Lys Asp Gly Lys Lys Glu Asp Cys Val Lys Gly 285 gac cct gtc gag aag gaa gcc aga gaa agt tct aag aaa gca gaa tct 1024 Asp Pro Val Glu Lys Glu Ala Arg Glu Ser Ser Lys Lys Ala Glu Ser 305 300 1076 gga gac caa aga aaa gga tta ctt tga agaaa gggccctcgt ctactggggc Gly Asp Gln Arg Lys Gly Leu Leu 315 ctctggtcaa gcaaagagct cttcaaagga atctaaagac agcaagacat catctaaaga 1136 tgacaaagga agtacaagta gtactagtgg tagcagtgga agctcaacta aaaatatctg 1196 ggttagtgga ctttcatcta ataccaaagc tgctgatttg aagaacctct ttggcaaata 1256 tggaaaggtt ctgagtgcaa aagtagttac aaatgctcga agtcctgggg caaaatgcta 1316 tggcattgta actatgtett caageacaga ggtgtecagg tgtattgeae atetteateg 1376 cactgagetg catggacage tgatttetgt tgaaaaagta aaaggtgate cetetaagaa 1436 agaaatgaag aaagaaaatg atgaaaagag tagttcaaga agttctggag ataaaaaaaa 1496 tacgagtgat agaagtagca agacacaagc ctctgtcaaa aaagaagaga aaagatcgtc 1556 tgagaaatct gaaaaaaaag aaagcaagga tactaagaaa atagaaggta aagatgagaa 1616 1656 gaatgataat ggagcaagtg gccaaacatc agaatcgatt <210> 119 <211> 906 <212> DNA

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aggccatgct aatcttactc tctgctccag ccttgaaact ggccatttt tcaaggagcc 180
agggttcttt ttctttggga acagttacca gcatctgagt atg ctc atc gtt tcg
Met Leu Ile Val Ser

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ggg tat ctc tgc ttc tgt gcc ctt cag tgg act gag cta gga aat gta 283 Gly Tyr Leu Cys Phe Cys Ala Leu Gln Trp Thr Glu Leu Gly Asn Val tgt gtg tgt gca cac ata tgc cgt tgc aca cac atg cag gtt tca ggg 331 Cys Val Cys Ala His Ile Cys Arg Cys Thr His Met Gln Val Ser Gly 30 atc aca agt ecg gtc cat gtc cac atc cat agg gtt ctt tct tgc ctt 379 Ile Thr Ser Pro Val His Val His Ile His Arg Val Leu Ser Cys Leu 45 atc cat ttc acc tct tag agcaga ggactttcac catttctatt gaacatgagt 433 Ile His Phe Thr Ser \* 55 ataatatgta gtccttacct aagaggattc tgtggatctt ctctggggtt ctcaggggcc 493 atggaacatg tcagagcaaa tgttggaatg gattacccag aatgtgagta gtgtgagtgg 553 ggcactgttg gactcagtcc caacccccta acgcgagttt gcatgaaaaa ttcatatctt 613 673 acttagggcc atcctaactt tcttgcttcc caaagggagg gtagatcaaa acataaggga aaggaggggt cataaacttg ttttgaaggt acccggggga accctaaaca ttataggggt 733 ctagtctatg gccgactagt cgcgactata aacgaagcct tcatcatagg gaaaaaggtg 793 caggactttc ttacacatgg ctagtagaac gggtctaggc tagcatgaga ccttccatgc 853

906

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ttt cct ctc cat ggt tac tct ggg agg cag aga ggt gct aag caa tgg 220 Phe Pro Leu His Gly Tyr Ser Gly Arg Gln Arg Gly Ala Lys Gln Trp 20

268 agg tgt cat ccg gcc cgc gca tct agg gaa cgt cct tca gag gac aac Arg Cys His Pro Ala Arg Ala Ser Arg Glu Arg Pro Ser Glu Asp Asn 35

ttg tca cca gcc gtc aaa gaa gag agt ggc ttt gtg gtc tct gaa cat 316

WU 01/33437	
Leu Ser Pro Ala Val Lys Glu Glu Ser Gly Phe Val Val Ser Glu His 45 50 55	
ctg gca gcg ctg cac agg aag ctg agg ggg tgt cat taa ttgtgatgaa Leu Ala Ala Leu His Arg Lys Leu Arg Gly Cys His * 60 65 70	365
ataatttaaa ccatcaggaa taaatgaggc tgttaagcta agttcagatt ccatttgcca	425
tgcacatgtg tctagcagcc tgtgtgcagt taaaagaaat tgaattatat tagctcatga	485
gtagaagtga aacagatact gtaaatgaaa caagttgctg tatagcgatg acatcgtgtt	545
gaaccatttc acagagttac agtttgtatg atcactgtat caaaagtggt atattattta	605
atgaattttt atattataaa acattcctac ggtatggagt atagtaagga ccagtggttt	665
atgggtaggt agagaggatg tgagctggat gggcagaaca aaacaatcca caggttacgg	725
gccttgaagg gagtgggagg gaaatcacgc gtcattggag cccagttgcc ctgttagagc	785
ccgaacggag tccacatcac gccgcctgca cttgggcata cgcgatcacg ggaacgctcc	845
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gtt atc tgt aag agt gga acc tct gtg aag atc gag tgc cgt tcc ctg Val Ile Cys Lys Ser Gly Thr Ser Val Lys Ile Glu Cys Arg Ser Leu	146

acc ttg tcc act ctg aca gtg acc agt gcc cat cct gaa gac agc agc
Thr Leu Ser Thr Leu Thr Val Thr Ser Ala His Pro Glu Asp Ser Ser

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90 95 100 105	
ttc tac atc tgc agt gct agt ggt atg aga cgc aca gat acg cag tat Phe Tyr Ile Cys Ser Ala Ser Gly Met Arg Arg Thr Asp Thr Gln Tyr 110 115 120	386
ttt ggc cca ggc acc cgg ctg aca gtg ctc gag gac ctg aaa aac gtg Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Lys Asn Val 125 130 135	434
ttc cca ccc gag gtc gct gtg ttt gag cca tca gaa gca gag atc tcc Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser 140 145 150	482
cac acc caa aag gcc aca ctg gtg tgc ctg gcc aca ggc ttc tac ccc His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro 155 160 165	530
gac cac gtg gag ctg agc tgg tgg gtg aat ggg aag gag gtg cac agt Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser 170 175 180	578
ggg gtc agc aca gac ccg cag ccc ctc aag gag cag ccc gcc ctc aat Gly Val Ser Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn 190 195 200	626
gac tee aga tae tge etg age age ege etg agg gte teg gee ace tte Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe 205 210 215	674
tgg cag aac ccc cgc aac cac ttc cgc tgt caa gtc cag ttc tac ggg Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly 220 225 230	722
ctc tcg gag aat gac gag tgg acc cag gat agg gcc aaa cct gtc acc Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr 235 240 245	770
cag atc gtc agc gcc gag gcc tgg ggt aga gca gac tgt ggc ttc acc Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr 250 265	818
tcc gag tct tac cag caa ggg gtc ctg tct gcc acc atc ctc tat gag Ser Glu Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu 270 275 280	866
atc ttg cta ggg aag gcc acc ttg tat gcc gtg ctg gtc agt gcc ctc Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu 285 290 295	914
gtg ctg atg gcc atg gtc aag aga aag gat tcc aga ggc tag ctccaaa Val Leu Met Ala Met Val Lys Arg Lys Asp Ser Arg Gly * 300 305 310	963
accateceag gteattette atceteacce aggattetee tgtacetget eccaatetgt	1023
gttcctaaaa gtgattctca ctctgcttct catctcctac ttacatgaat acttctctct	1083
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                                                                      60
geoctaagtg gttgagagtt cacaaacacc actecetece tgaggactaa cagecattga
                                                                     120
ctactggtct gcttgttaac tgactctcca gagctcccca tgagct
                                                     atg agt gtg
                                                                     175
                                                     Met Ser Val
gga ctt cac ctg gga ttt ctt gct tgg ttt ctt ccc ttt cta att ccc
                                                                     223
Gly Leu His Leu Gly Phe Leu Ala Trp Phe Leu Pro Phe Leu Ile Pro
                         10
                                             15
act tet eee ett eee tta eta ttt eaa etg gga gea ett eet aat gaa
                                                                     271
Thr Ser Pro Leu Pro Leu Leu Phe Gln Leu Gly Ala Leu Pro Asn Glu
tea ett gea ett tat get tgg ete agg gat tge tte tgg gag aac ata
                                                                      319
Ser Leu Ala Leu Tyr Ala Trp Leu Arg Asp Cys Phe Trp Glu Asn Ile
                                     45
acc taa aatgtccaac aataaggaac agttaatgac atccatccaa cacaatatcc
                                                                     375
Thr *
tttggctgtt aagaacctat ctctgaagaa aacttaaaga catggtaata cattctggat
                                                                      435
atatcttaac tggaaaaaag tatggcataa ttaactatgt aaaaattata cacaggcaca
                                                                     495
aattatocag gtgtggtggc gggtgcttgt actgccagct acttgggagg ctgaggcagg
                                                                     555
agaatggcgt gaacccagga ggcggagctt gcagtgagcc gagatcccac cactggactc
cattetggcg aaagagcaga gactegteec aaaaaaaaga aaaaaaaggt tgtttttgag
                                                                     675
gggccggcgg tttttccttt tggggggtaa aattattggg cctgqqcqqq qtttaaaacq
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                                                                        60
                                                                       109
tctattcttt gttgat
                     atg gaa aaa tat ttt cac aca gtt atg atc aag
                     Met Glu Lys Tyr Phe His Thr Val Met Ile Lys
                                        5
                                                           10
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<210> 124

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gtt tt Val Le	g gga u Gly 30	Asp	att Ile	gct Ala	ata Ile	gac Asp 35	tac Tyr	att Ile	att Ile	gtt Val	ccc Pro 40	aat Asn	att Ile	tcc Ser	205
tac ct Tyr Le 4	u Ser	ata Ile	tct Ser	ata Ile	ccc Pro 50	ttt Phe	gta Val	gtt Val	act Thr	aac Asn 55	att Ile	aga Arg	ggt Gly	aga Arg	253
gat at Asp Il 60	t tto e Phe	cac His	ccc Pro	tgt Cys 65	aat Asn	gtg Val	gcc Ala	ttg Leu	gtc Val 70	atg Met	tga *	ctt	ggaa	tgt	302
tagtag	ttct	gatgi	tgcad	ca g	aggc	tgta	c at	ggac	tttc	agc	attg	ggt	ttac	tetete	362
gggttt	ctgc	tgtt	tccat	ta c	aaag	aatg	t ac	cctg	ggtg	gcc	cacc	agc	cact	gagata	a 422
tgtgaa	tcca	actt	gaaci	tc a	actc	atgg	c ct	ggag	ccaa	gtt	ccac	cag	tcct	aactag	482
cttago	caaa	atcc	agct	ga t	ctga	aagt	g ca	tgaa	tgag	aaa	taaa	agc	ttat	tattt	542
ttttan	nann	aann	annn	aa a	aaaa	aaag	a ct	tttt	ttta	<b>a</b> aa	aaaa.	<b>9</b> 99	gggt	tttcto	602
cttttc	gagg	3 <b>3</b> 33	aaat	ta a	taaa	atga	g tg	gcgc	cccc	ctc	ttcc	ctt	gcgc	gaggg	g 662
gtaaaa	ıggcc	cggn	nnnn	nn c	cggc	cccc	c cc	ccgc	cccc	ccc	cccc	ggc	ggaa	agccgg	722
aaaagg	nggg	<b>a</b> aaa	ggng	gg g	ngaa	gtgg	g gt	gtcc	cccc	ccc	cacc	ccc	cccc	ccacta	a 782
at															784

<210> 125

<211> 597

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (314)..(463)

<400> 125

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Tyr Leu Gln Asp Met Leu Leu Ser Tyr Arg Leu Leu Val Ala Ile Leu

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15 20 25	·
gtt ttg ctg aag aaa tta aca gaa ctt aat aca att act ctt att tgc Val Leu Leu Lys Lys Leu Thr Glu Leu Asn Thr Ile Thr Leu Ile Cys 30 40	445
aag tot ata att tto taa acotaa ototgatgoa gtootactoo taatatttao Lys Ser Ile Ile Phe * 45 50	499
aaggcctaga acaagagtat ataaatggca gcccacattc tacgggtcta aatatataca	559
agttataaac caagtcagca aaataaaatg ccatgtat	597
<210> 126 <211> 580 <212> DNA <213> Homo sapiens	
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ggtaaaatct gctccgacca gagagaaaaa actaattcat at atg aat ata gta Met Asn Ile Val 1	174
ttt gta atc ctc ttg ttt aaa gac atg caa gtt cta gaa gta ttt gta Phe Val Ile Leu Leu Phe Lys Asp Met Gln Val Leu Glu Val Phe Val 5 10 15 20	222
ctg ctt aat gtt tta aca act cta aca ata ata gca gcg ggc ata ctt Leu Leu Asn Val Leu Thr Thr Leu Thr Ile Ile Ala Ala Gly Ile Leu 25 30 35	270
tgt acc agt ttt tgc tgt aag cct ttt ata tat att aat cct ctt taa Cys Thr Ser Phe Cys Cys Lys Pro Phe Ile Tyr Ile Asn Pro Leu * 40 45 50	318
aaccacccta tcaagtacaa gataataatt tgatatggtt gatgaagcaa ctgatgggaa	378
aaaagagagg ttaaataatt tgccccaaat cttattaagt gatgtagcca gcatctgaac	438
ccaatcagac tgtagactag agcctcctcc caaccactca gctttgctgc ttcccacata	498
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Met Thr Asn Phe Phe His Leu Leu Pro Leu Leu Pro Ser Leu
1 5 10 15

ttt Phe																	155
atc Ile																	203
ctt Leu			Arg														251
gaa Glu	tgg Trp 65	atc Ile	acc Thr	tct Ser	ata Ile	agg Arg 70	tgc Cys	tta Leu	tgt Cys	aac Asn	tct Ser 75	gga Gly	act Thr	acg Thr	ttt Phe		299
ata Ile 80								aca Thr		g to	cata	cttai	t tt	ttate	gtet		350
cagg	cta	cta a	aaat	agaa	ca t	gttc	tctag	g agg	gaga	aċat	caa	ggag	ttc 1	tttta	atttgt	=	410
cg																	412

<210> 129

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<212> DNA

<213> Homo sapiens

<220>

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ccctgcccac cgaggccag	c acctgggtga	agttgcgtca	tccaaaggcg gccacg	ggagc 840
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aaggacgtat ctgtggact	t cactcaggag	gagtgggggc	agetggeeee tgetea	accgg 960
aatctgtacc gggaggtg	atg ctg gag Met Leu Glu 1	g aac tat ggg n Asn Tyr Gly 5	g aac ctg gtc tca / Asn Leu Val Ser 10	gtg 1011 Val
gga tgt cag ctt tcc Gly Cys Gln Leu Ser 15	aaa cct ggc Lys Pro Gly	gtg att tcc Val Ile Ser 20	cag ttg gag aaa g Gln Leu Glu Lys G 25	gga 1059 Gly
gaa gaa cca tgg ctg Glu Glu Pro Trp Leu 30	atg gag aga Met Glu Arg 35	gat att tca Asp Ile Ser	gga gtt cca agt Gly Val Pro Ser 40	tca 1107 Ser
gac ttg aag agc aaa Asp Leu Lys Ser Lys 45	aca aaa acc Thr Lys Thr 50	aaa gag tca Lys Glu Ser	gcc tta cag aat Ala Leu Gln Asn 55	gat 1155 Asp
att tcg tgg gaa gaa Ile Ser Trp Glu Glu 60	cta cat tgt Leu His Cys 65	ggc cta atg Gly Leu Met 70	atg gaa aga ttt Met Glu Arg Phe	aca 1203 Thr 75
aaa gga agc agc atg Lys Gly Ser Ser Met 80	tat tcc acc Tyr Ser Thr	ttg gga aga Leu Gly Arg 85	atc tcc aaa tgt Ile Ser Lys Cys 90	aat 1251 Asn
aag cta gaa agc caa Lys Leu Glu Ser Gln 95	caa gag aac Gln Glu Asn	caa aga atg Gln Arg Met 100	ggt aag ggg caa Gly Lys Gly Gln 105	atc 1299 Ile
ccc ctg atg tgc aag Pro Leu Met Cys Lys 110	aaa aca ttc Lys Thr Phe 115	Thr Gln Glu	aga ggc caa gag Arg Gly Gln Glu 120	tct 1347 Ser
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cca ata ggt ctt cca Pro Ile Gly Leu Pro 140	aga aaa aga Arg Lys Arg 145	Asp Arg Lys	Tyr Asp Thr Pro	gga 1443 Gly 155
aag aga agc aga tac Lys Arg Ser Arg Tyr 160	Asn Ile Asp	tta gtt aat Leu Val Asn 165	cat tca agg agt His Ser Arg Ser 170	tat 1491 Tyr
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cag ctt att cac ctt Gln Leu Ile His Leu 190		Met Arg Ile		
cct ttc aga tgt aag Pro Phe Arg Cys Lys 205				
ctt att ccg cat cag Leu Ile Pro His Glr				

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aag gag tgt ggg Lys Glu Cys Gly	aaa acc ttc Lys Thr Phe 240	aga cat cct Arg His Pro 245	tca tcg ctt act Ser Ser Leu Thr	caa cat 1731 Gln His 250				
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cag att aga cac Gln Ile Arg His 300	ctt agg caa Leu Arg Gln 305	cat gag att His Glu Ile	att cat act ggt Ile His Thr Gly 310	gtg aaa 1923 Val Lys 315				
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cag aga gtc cat Gln Arg Val His 365	act gga gta Thr Gly Val 370	aaa cct tat Lys Pro Tyr	gaa tgc agt cat Glu Cys Ser His 375	tgt ggg 2115 Cys Gly				
			aaa cat cag aga Lys His Gln Arg 390					
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PCT/US01/02623

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cct tcc cat cat tca ggt ttc agt tca aat gag gct tct ctg agg act 632 Pro Ser His His Ser Gly Phe Ser Ser Asn Glu Ala Ser Leu Arg Thr

Met Pro Cys Ser Val Pro Glu Thr Leu Phe Ser Leu Leu Trp Leu Ala

gat cta tta ttt gcc aca gcc att ctt tat tct cta tgg cat cct cca 680 Asp Leu Leu Phe Ala Thr Ala Ile Leu Tyr Ser Leu Trp His Pro Pro 40

tat tat ttt ctt tat aat act tct taa tgtgt gaataattac tgtgtggatg 732 Tyr Tyr Phe Leu Tyr Asn Thr Ser 50 55

acttocttac atagttattt atttgttaat gttcttgctt acatttcatt gtcagcttct 792 agaagaagag ctctttaaga gcagtgaccc tgtctgtctt gatcatggaa caaagactgg 852 tatatccaga tgttcaataa atattttcct gtatgaatac atgactatgt ttt 905

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Met Leu Phe Thr Ser Phe Val Tyr Gly Leu att ttt att ttg ttt gat ttt tat ttt cta tca ttt gtt gaa agg gat 218 Ile Phe Ile Leu Phe Asp Phe Tyr Phe Leu Ser Phe Val Glu Arg Asp 15 gtt aaa atc ttc aac tgt aat ggt gaa ata gta ttg ttt cca ttt aat 266 Val Lys Ile Phe Asn Cys Asn Gly Glu Ile Val Leu Phe Pro Phe Asn 30 tot gtt cat ttt tgc ctg ata tgt ctt tat ata cac att taa gattatg 315 Ser Val His Phe Cys Leu Ile Cys Leu Tyr Ile His Ile \* 45 50 55 tetteetgat gagttgtgaa ttagaacatt atgaaatgtt atteteeggg aatattatte 375 teteettaca gtetatttta eteaatattg atatageaac teeateettt atataettae 435 tgtttacatg gtgtgccttt tcagaagcat ttactttcaa ttatagatag catatagatg 495 agacttgttt ttttttaaat ctattctgaa aatttctgat tttattatta ggaatattta 555 ggggaaatgt ttaataaatt aatattttgg gtttttcttt ctgccatttt tcatatttat ccctcctcct cccccaggaa aaattcaaaa ctcttttctt caaactagta cgaaggataa 675 aaatacgctt ccccaccact cgtgggctcc tctctcatcg tcaccctttc ttacaactct 735 caaaccccc ttacataata tcctctggac cctcaacctc tcatqtqctq caattcqccq 795 acaactttct gtctcccgcc atttcacctt ccatctcctg ccaacctgaa gcctccgctc 855 getateactt ttgctatate acctettete aacctaceta etatacagte cagettetet 915 tcattaggta gattcttcaa tatatactcc tcgctaaacc tacaccctag cgccctgaac 975 tactccccc gcatcccact ccaagctccg cacctatcct ctccacgact aatacgctat 1035

1069

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10

<210> 132

15

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<223> n = a,t,c or g
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aaaacttc atg tgt tta att ctg gtt atc tgg aaa att cac tat gca gaa Met Cys Leu Ile Leu Val Ile Trp Lys Ile His Tyr Ala Glu 1 5 10	170
ctt ata atg tta aat aaa cga gtt gtt aat aaa tgt aga tca tgt ctt Leu Ile Met Leu Asn Lys Arg Val Val Asn Lys Cys Arg Ser Cys Leu 15 20 25 30	218
atc caa aaa tgc cta tct aca tgt cat agt aca gtc att gtt tta tat Ile Gln Lys Cys Leu Ser Thr Cys His Ser Thr Val Ile Val Leu Tyr 35 40 45	266
caa tgc aga gag gaa gaa gct gtg atg tta ata aag ttg aat ttt aaa Gln Cys Arg Glu Glu Glu Ala Val Met Leu Ile Lys Leu Asn Phe Lys 50 55 60	314
atg aaa atc caa aga act ata tgt ata tag g ccaaataaaa agttacttga Met Lys Ile Gln Arg Thr Ile Cys Ile * 65 70	365
ttacttaata atatggatta aaatgagtaa tcactgtaat tcatatattc aagaagtttt	425
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cat ttc ccc att tcc att tat gac aac att ggt cat tgg cct cag tca His Phe Pro Ile Ser Ile Tyr Asp Asn Ile Gly His Trp Pro Gln Ser 30 35 40	206
ccg aaa gtc agg agg aag gaa gga aat gaa tat tta ttg aac ccc aat Pro Lys Val Arg Arg Lys Glu Gly Asn Glu Tyr Leu Leu Asn Pro Asn 45 50 55 60	254
atg tgc cag acc ctg gat tta aca ctt tta ggg ata gga gat tat tta Met Cys Gln Thr Leu Asp Leu Thr Leu Leu Gly Ile Gly Asp Tyr Leu 65 70 75	302
acc tca ata acc tct ccc tga gg gcaggaagtg gatttataga tgcggaaaca Thr Ser Ile Thr Ser Pro * 80	355 ·

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gatcctacag	cctgcccata	acacccctgg	caaccacccg	tccccaccgc	gcccacccac	715
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ttt tet tet et et eage act tre eet ggg tgg ttg ett ate ate tge aca
471
Phe Ser Ser Leu Ser Thr Phe Pro Gly Trp Leu Leu Ile Ile Cys Thr
75 80 85

ctg atg att taa aca tagagttttt geetgtatet etcecectaa gtetaggett
Leu Met Ile \*

Gln Leu Ser Leu Leu Met Gly Thr Ser Ala Val Cys Leu Ser Ala Cys

90

60

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tggacacatt tattaccagt tttattcaaa aattaaacat ttgttcagca tttgtgtcct

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684

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aactgtgaac atctgatctt gatactggct t atg ttg tct ctt gtt aag ctt 232 Met Leu Ser Leu Val Lys Leu 1 5

ttg ctt ctt tgc att att cat gac cat tca att aat ttt tgt ata gcc 280 Leu Leu Cys Ile Ile His Asp His Ser Ile Asn Phe Cys Ile Ala 10 15 20

ata cag gta gga tta tta cca agt gcc tac cgt gta cca gga ata gtt

11e Gln Val Gly Leu Leu Pro Ser Ala Tyr Arg Val Pro Gly Ile Val

25

30

328

cta agc ctt gag aat aca gca cta ata agg cag act ccc tgc tca aat

376
Leu Ser Leu Glu Asn Thr Ala Leu Ile Arg Gln Thr Pro Cys Ser Asn

40

50

55

aga gcc aac taa tga aaaatcgata aaatagagac taaagagaga teettagttg 431 Arg Ala Asn \*

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aaaaatctgg ttgtcctccg taacacctgc gataagacga tcgacggtag gtctatatcg 671

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<211> 1126

<212> DNA

<213> Homo sapiens

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<221> CDS

<222> (144)..(707)

<400> 138

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Met Arg Pro Leu Ala Gly Ala Pro Val

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gcc aga gga ata aac att gcc att gtc aac tat gta act ggg a Ala Arg Gly Ile Asn Ile Ala Ile Val Asn Tyr Val Thr Gly A 60 65 70	at gtg 362 sn Val
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tct agc tgg gta ttt att gca gca aaa ggc ttg gaa ctc cct t Ser Ser Trp Val Phe Ile Ala Ala Lys Gly Leu Glu Leu Pro S 140 145 150	cc gaa 602 Ser Glu
att cag aga gaa aag atc aac cac tct gat gct aag aac aac a Ile Gln Arg Glu Lys Ile Asn His Ser Asp Ala Lys Asn Asn A 155 160 165	
tct ggc tgg cct gca gag atc cag ata gaa ggc tgc ata ccc a Ser Gly Trp Pro Ala Glu Ile Gln Ile Glu Gly Cys Ile Pro I 170 175 180	aaa gaa 698 ays Glu 185
cga agc tga cactgca gggtcctgag taaatgtgtt ctgtataaac aaat Arg Ser *	gcagct 754
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115 120 125

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														att Ile		1064
														tac Tyr		1112
					_	_								atg Met	-	1160
_	_			_	_				_		_	_		gac Asp	-	1208
														caa Gln 240		1256
_		-		_				-	-	-		_		cac His		1304
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_				_			_		-			_	-	aac Asn	-	1400
			_	_	_							_	_	gct Ala		1448
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370 375	380	385
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gaattgette tatteaaaat gea	agacaca atg cca ggt gtt ggt Met Pro Gly Val Gly 1 5	Leu Leu Val
tcc cat ttt tca acc ctc o Ser His Phe Ser Thr Leu 10	gtt tct agg caa agg tgt cca Val Ser Arg Gln Arg Cys Pro 15 20	aat tat gca 221 Asn Tyr Ala
gac cca cag aat cta aca q Asp Pro Gln Asn Leu Thr i 25	gat gtc tct ata ttc ctc ctc Asp Val Ser Ile Phe Leu Leu 35	cta gaa gtc 269 Leu Glu Val 40
tca ggg gat cca gaa ctg ( Ser Gly Asp Pro Glu Leu ( 45	cag cca gtc ctt gct ggg ctg Gln Pro Val Leu Ala Gly Leu 50	ttc ctg tcc 317 Phe Leu Ser 55
atg tgc ctg gtc acg gtg 6 Met Cys Leu Val Thr Val 1 60	ctg ggg aac ctg ctc atc atc Leu Gly Asn Leu Leu Ile Ile 65	ctg gcc atc 365 Leu Ala Ile 70
age ect gae tee cae ete e Ser Pro Asp Ser His Leu F 75	cac acc ccc atg tac ttc ttc His Thr Pro Met Tyr Phe Phe 80 85	ctc tcc aac 413 Leu Ser Asn
ctg tcc ttg cct gac atc c Leu Ser Leu Pro Asp Ile ( 90	ggt ttc acc tcc acc acg gtc Gly Phe Thr Ser Thr Thr Val 95 100	ccc aag atg 461 Pro Lys Met
att gtg gac atc cag tct of fle Val Asp Ile Gln Ser I	cac agc aga gtc atc tcc tat His Ser Arg Val Ile Ser Tyr 115	gca ggc tgc 509 Ala Gly Cys 120

ctg act cag atg tct ctc ttt gcc att ttt gga ggc atg gaa gag aga Leu Thr Gln Met Ser Leu Phe Ala Ile Phe Gly Gly Met Glu Glu Arg 125 130 135	557
cat gct cct gag tgt gat ggc cta tga ctggt ttgtagccat ctgtcacccg His Ala Pro Glu Cys Asp Gly Leu * 140 145	609
ctatateatt caccateatg aaccegtgtt tetgtgeett tetagttttg ttgtettttt	669
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WO 01/5	5 <b>45</b> 1									_		
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tgc ccc Cys Pro 210	tca Ser	cgg ( Arg (	tcc Ser	tca Ser 215	aac Asn	cct Pro	Gly ggg	ctg Leu	ctg Leu 220	gag Glu	ctg Leu	cct Pro	cga Arg	gtg Val 225	1748
cac gtg His Val		Asp (													1796
ggc tcc Gly Ser	Gln												Gly		1844
ggc acc Gly Thr															1892
gct gga Ala Gly 275															1940
ata gtg Ile Val 290	agg	tcc t Ser (	Cys	agg Arg 295	aag Lys	aaa Lys	tcg Ser	gca Ala	agg Arg 300	cca Pro	gca Ala	gcg Ala	ggc Gly	gtg Val 305	1988
ggg gat Gly Asp	aca (	Gly N	atg Met 310	gaa Glu	gat Asp	gca Ala	aag Lys	gcc Ala 315	atc Ile	agg Arg	ggc Gly	tcg Ser	gcc Ala 320	tct Ser	2036
cag gga Gln Gly	Pro 1	ctg a Leu 1 325	act Thr	gaa Glu	tcc Ser	tgg Trp	aaa Lys 330	gat Asp	ggc Gly	aac Asn	ccc Pro	ctg Leu 335	aag Lys	aag Lys	2084
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gaa act Glu Thr	gca g Ala (	3lu T	hct Thr 190	cag Gln	gcc Ala	tgt Cys	Leu	agg Arg 395	aat Asn	cac His	aac Asn	ccc Pro	tcc Ser 400	agc Ser	2276
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cctttccc															2450
tctcgaco															2510
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actotoogot gatgoootto atgootaago atgotooogg too atg cac tgo aga · Met His Cys Arg 1	
cag tta aag gaa gtg ctg cag ctt cct tta acc tgc agc agc tgc tgt Gln Leu Lys Glu Val Leu Gln Leu Pro Leu Thr Cys Ser Ser Cys Cys 5 10 15 20	283
gtc tgt acc atg acc gtg gca ttt ccc agc gtc cag cag gtg tgg atg Val Cys Thr Met Thr Val Ala Phe Pro Ser Val Gln Gln Val Trp Met 25 30 35	331
gag act gtg ctg act ctg ggt ggg ctt gat gct gct cag gat gag atc Glu Thr Val Leu Thr Leu Gly Gly Leu Asp Ala Ala Gln Asp Glu Ile 40 45 50	379
cag gcg gtg agg ctc att ctc ctc cct gag tcc tct cct cag ggg cca Gln Ala Val Arg Leu Ile Leu Leu Pro Glu Ser Ser Pro Gln Gly Pro 55 60 65	427
cat ggg aac ctg gct ccc tgt tct gca aag ccc ttc ttc ctt ccc caa His Gly Asn Leu Ala Pro Cys Ser Ala Lys Pro Phe Phe Leu Pro Gln 70 75 80	475
gtc atg ccc ttg ggc aca gcc cct tag ggcta ggggcettca ccctcaggca Val Met Pro Leu Gly Thr Ala Pro * 85 90	527
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Leu Thr Val Glu Trp Arg Ala Arg Ser Glu Ser Ala Gln Ser Lys Met	
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85 90 95

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aat Asn	cag Gln 115	gtt Val	aac Asn	gag Glu	ctc Leu	atg Met 120	aat Asn	aga Arg	gtt Val	ctc Leu	ctt Leu 125	ttg Leu	act Thr	aca Thr	gaa Glu	440
gtt Val 130	ttt Phe	aga Arg	aaa Lys	cag Gln	ctg Leu 135	gat Asp	cct Pro	ttt Phe	cct Pro	cac His 140	aga Arg	cct Pro	gtt Val	cag Gln	tca Ser 145	488
cat His	ggt Gly	tta Leu	gat Asp	tgc Cys 150	act Thr	gat Asp	att Ile	aag Lys	gat Asp 155	acc Thr	att Ile	ggc Gly	tct Ser	gtc Val 160	acc Thr	536
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gat Asp	gtt Val	gat Asp	aat Asn 245	gat Asp	Gly 999	tgt Cys	cgc Arg	cct Pro 250	gca Ala	tgc Cys	ctg Leu	gtc Val	aat Asn 255	ggt Gly	cag Gln	824
tct Ser	gtg Val	aag Lys 260	agc Ser	tgc Cys	agt Ser	cac His	ctc Leu 265	cat His	aac Asn	aag Lys	acc Thr	ggc Gly 270	tgg Trp	tgg Trp	ttt Phe	872
							Leu							tct Ser		920
	_		_							_	-			aac Asn		968
														atg Met 320		1016
	cca Pro				taa	tctc	att	taac	attg	ta a	tgca	agtt	c ta	caat	gata	1071
ata	tatt	aaa	gatt	ttta	aa a	gttt	atct	t tt	cact	tagt	gtt	tcaa	aca	tatt	aggcaa	1131

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PCT/US01/02623 WO 01/55437

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caat	atgo	cc 9	ī													737
	<21 <21	.0> 1 .1> 1 .2> I	.255 NA	sapi	.ens											
		1> 0		(121	.7)											
cc	ato	Ala	ago	tcg Ser	. GJ <sup>7</sup>	Pro	g gcc Ala	atg Met	g ctt	cgo Arg	g Gly	ccg Pro	tgg Tr	g cgc o Arg	ttt Phe 15	47
ttt Phe	tgg Trp	ctc Leu	ttt Phe	ctc Leu 20	ctg Leu	ctg Leu	ctg Leu	ctc Leu	ccg Pro 25	ggc Gly	gcg Ala	ccc Pro	gac Asp	cca Pro 30	cgc Arg	95
gtc Val	cgc Arg	tcc Ser	agg Arg 35	ccg Pro	tgg Trp	gag Glu	gga Gly	acc Thr 40	gac Asp	gag Glu	ccg Pro	ggc Gly	tcg Ser 45	gcc Ala	tgg Trp	143
gcc Ala	tgg Trp	ccg Pro 50	ggc Gly	ttc Phe	cag Gln	cgc Arg	ctg Leu 55	cag Gln	gag Glu	cag Gln	ctc Leu	agg Arg 60	gcg Ala	gcg Ala	ggt Gly	191
gcc Ala	ctc Leu 65	tcc Ser	aag Lys	cgg Arg	tac Tyr	tgg Trp 70	acg Thr	ctc Leu	ttc Phe	agc Ser	tgc Cys 75	cag Gln	gtg Val	tgg Trp	ccc Pro	239
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cgc Arg	ctt Leu	cct Pro	ctg Leu	ttg Leu 100	ggc Gly	cag Gln	cgg Arg	tac Tyr	ctg Leu 105	gac Asp	ctc Leu	ctg Leu	acc Thr	acg Thr 110	tgg Trp	335
tac Tyr	tgc Cys	agc Ser	ttc Phe 115	aaa Lys	gac Asp	tgc Cys	tgc Cys	cct Pro 120	aga Arg	GJ À GGA	gat Asp	tgc Cys	aga Arg 125	atc Ile	tcc Ser	383
					tta Leu											43]
					cag Gln											479
					gaa Glu 165											527
tct Sér	ggc Gly	aca Thr	ggc Gly	aag Lys	aac Asn	ttc Phe	gtg Val	gca Ala	cgg Arg	atg Met	ctg Leu	gtg Val	gag Glu	aac Asn	ctg Leu	575

180 185 623

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ttc cac ttt cct cac ccc aaa tat gtg gac ctg tac aag gag cag ctg 671 Phe His Phe Pro His Pro Lys Tyr Val Asp Leu Tyr Lys Glu Gln Leu 215

atg age cag atc cgg gag acg cag cag ctc tgc cac cag acc ctg ttc 719 Met Ser Gln Ile Arg Glu Thr Gln Gln Leu Cys His Gln Thr Leu Phe 230

atc ttc gat gaa gcg gag aag ctg cac cca ggg ctg ctg gag gtc ctt 767 Ile Phe Asp Glu Ala Glu Lys Leu His Pro Gly Leu Leu Glu Val Leu 250 245

ggg cca cac tta gaa cgc cgg gcc cct gag ggc cac agg gct gag tct 815 Gly Pro His Leu Glu Arg Arg Ala Pro Glu Gly His Arg Ala Glu Ser 260

cca tgg act atc ttt ctg ttt ctc agt aat ctc agg ggc gat ata atc 863 Pro Trp Thr Ile Phe Leu Phe Leu Ser Asn Leu Arg Gly Asp Ile Ile 280 275

aat gag gtg gtc cta aag ttg ctc aag gct gga tgg tcc cgg gaa gaa 911 Asn Glu Val Val Leu Lys Leu Leu Lys Ala Gly Trp Ser Arg Glu Glu 295

att acg atg gaa cac ctg gag ccc cac ctc cag gcg gag att gtg gag 959 Ile Thr Met Glu His Leu Glu Pro His Leu Gln Ala Glu Ile Val Glu 310

1007 acc ata gac aat ggc ttt ggc cac agc cgt ctt gtg aag gaa aac ctg Thr Ile Asp Asn Gly Phe Gly His Ser Arg Leu Val Lys Glu Asn Leu 325 330

att gac tac ttc atc ccc ttc ctg cct ttg gag tac cgt cac gtg agg 1055 Ile Asp Tyr Phe Ile Pro Phe Leu Pro Leu Glu Tyr Arg His Val Arg 340

ctg tgt gca cgg gat gcc ttc ctg agc cag gag ctc ctg tat aaa gaa 1103 Leu Cys Ala Arg Asp Ala Phe Leu Ser Gln Glu Leu Leu Tyr Lys Glu 360 355

gag aca ctg gat gaa ata gcc cag atg atg gtg tat gtc ccc aag gag 1151 Glu Thr Leu Asp Glu Ile Ala Gln Met Met Val Tyr Val Pro Lys Glu 375 370

gaa caa ctc ttt tct tcc cag ggc tgc aag tct att tcc cag agg att 1199 Glu Gln Leu Phe Ser Ser Gln Gly Cys Lys Ser Ile Ser Gln Arg Ile 390 385

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ata tga aatcttatag ctcagatatg aaggaaactt agcagtttcc ccagatttga

4	5

caattctaaa aattacatgg tgctactaat acatagttga ggatgtaaaa gaagcctcta 320 taaactgcca aaaagaaaaa taaaaaggga ttttccatta aaaatgtatg tgctatgtaa 380 440 ttgcccaggc tggagtgtaa tggggccatc tcggcttgct gcaacctcca cctcctgggt 500 560 tcaagcgatt ctccagcctc agcctcccaa gtggctgaga ttgcaggcac cgccaccacc cccgcaaaat tttggaattt taagaagata gggggttcca cattttggcc cggctgggtc 620 taaacttcct gatccaccaa cttaaccctc caaagggcgt ggataacagg gggagccacc 680 cgccctgcca gaatatgaat ttttaaatgg atgtttggag gcacactaca tatttcctag 740 actacttccg atatttttt acggggaacc tatattttac ccattggaaa taaaaaaaaa 800 836 atattttatt ttaaaaagga ggattggccc ctgggc

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1 5

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Gly Met Ser Leu Leu Cys Leu Thr Asp Val Phe Gln Ala Leu Pro Ser

10 15 20

ata tgt att gcg aat agt gag att tat tac aca gtc cta aca ttg atg 149

Ile Cys Ile Ala Asn Ser Glu Ile Tyr Tyr Thr Val Leu Thr Leu Met

30 35

cag ttt agt tgc ttg tgg atg gtg ttg tca gga aaa aag gta ata ttt 197 Gln Phe Ser Cys Leu Trp Met Val Leu Ser Gly Lys Lys Val Ile Phe 40 45 50 55

tct tct gaa ctc atg gtt aga aag ggc agg aga agc tgg aag taa gat 245 Ser Ser Glu Leu Met Val Arg Lys Gly Arg Arg Ser Trp Lys \*

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tgactggaaa	gaagcagcac	gagtgaatgg	atggaaatga	aaaaaagatc	tacagagata	725
tccactgcaa	gaggagtttt	catcgccagg	gcaccagctt	ctccagttac	cttcccctgt	785
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atcatctatg atacattaac atatatctga tgatacatta gctgatgata tatgctatga 180

tatattagca tattctaatt agcatatatc atcagcatat atgggaatgt cattggc 237

atg tat ttg aag ccc tta ata tac ttt tct att ttg ata ttt ttg agt 285

Met Tyr Leu Lys Pro Leu Ile Tyr Phe Ser Ile Leu Ile Phe Leu Ser 1 5 10 15

caa agg agt aaa tta tcc ctt ccc tac aat gtt cac aat tgt atg aat

Gln Arg Ser Lys Leu Ser Leu Pro Tyr Asn Val His Asn Cys Met Asn

20 25 30

ata ggt gaa gat agg cga ccc cag aaa gta cag ctg ctt cag ttg tac

Ile Gly Glu Asp Arg Arg Pro Gln Lys Val Gln Leu Leu Gln Leu Tyr

35 40 45

taataagtaa tcatcatcct gcaagaagta tgttgtgact tctcctacaa ttaactatca 441

gcaaggatta gattgcaata attattatat ttataatttc tagcatgttt ggggggggga 561
ccatttgagg ttcctaaacc aatggggcgg gttttttaaa aaccaaaacc ttcccacaaa 621
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tataqtttaa tatatgttta atattattat aaaaagtaga aaaataaaat ttatttagaa

501

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gaagggtaaa acccaaggcg gggccttggt tctggcagaa gggacgct atg acc gca Met Thr Ala 1

gaa ttc ctc tcc ctg ctt tgc ctc ggg ctg tgt ctg ggc tac gaa gat 225
Glu Phe Leu Ser Leu Leu Cys Leu Gly Leu Cys Leu Gly Tyr Glu Asp
5 10 15

gag aaa aag aat gag aaa ccg ccc aag ccc tcc ctc cac gcc tgg ccc
Glu Lys Lys Asn Glu Lys Pro Pro Lys Pro Ser Leu His Ala Trp Pro
20 25 30 35

age teg gtg gtt gaa get gag age aat gtg ace etg aag tgt eag get

Ser Ser Val Val Glu Ala Glu Ser Asn Val Thr Leu Lys Cys Gln Ala

40

45

50

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tac Tyr	aag Lys	cag Gln 70	gaa Glu	cag Gln	agc Ser	tcg Ser	gca Ala 75	gaa Glu	aac Asn	gaa Glu	gct Ala	gaa Glu 80	ttc Phe	ccc Pro	ttc Phe	417
acg Thr	gac Asp 85	ctg Leu	aag Lys	cct Pro	aag Lys	gat Asp 90	gct Ala	Gly 999	agg Arg	tac Tyr	ttt Phe 95	tgt Cys	gcc Ala	tac Tyr	aag Lys	465
				cat His												513
gtg Val	gtc Val	aca Thr	gat Asp	aaa Lys 120	cac His	gat Asp	gaa Glu	ctt Leu	gaa Glu 125	gct Ala	ccc Pro	tca Ser	atg Met	aaa Lys 130	aca Thr	561
				ata Ile												609
				tca Ser												657
				gaa Glu												705
				gcc Ala												753
	_	_	_	gac Asp 200							-					801
_	_	_		gag Glu	-	_		_			_					849
		-		gcg Ala	, —	-			tag *	c a	aaaa	gaca	g cc	ctgg	ccac	900
taa	agga	ggg (	ggga	tcgt	gc t	ggcc	aagg	t ta	tegga	aaat	ctg	gaga	tgc (	agat	actgtg	960
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ccc ctg ctg aca ctc tac ctg ctc ctc ttc tgg ctc tca ggc tac tcc Pro Leu Leu Thr Leu Tyr Leu Leu Leu Phe Trp Leu Ser Gly Tyr Ser 5 10 15	164
att gtc act caa atc acc ggt cca aca aca gtg aat ggc ttg gag cgg Ile Val Thr Gln Ile Thr Gly Pro Thr Thr Val Asn Gly Leu Glu Arg 20 25 30	212
ggc tcc ttg acc gtg cag tgt gtt tac aga tca ggc tgg gag acc tac Gly Ser Leu Thr Val Gln Cys Val Tyr Arg Ser Gly Trp Glu Thr Tyr 35 40	260
ttg aag tgg tgg tgt cga gga gct att tgg cgt gac tgc aag atc ctt Leu Lys Trp Trp Cys Arg Gly Ala Ile Trp Arg Asp Cys Lys Ile Leu 50 65	308
gtt aaa acc agt ggg tca gag cag gag gtg aag agg gac cgg gtg tcc Val Lys Thr Ser Gly Ser Glu Gln Glu Val Lys Arg Asp Arg Val Ser 70 75 80	356
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ctc atg aaa act gat gct gac act tac tgg tgt gga att gag aaa act Leu Met Lys Thr Asp Ala Asp Thr Tyr Trp Cys Gly Ile Glu Lys Thr 100 105 110	452
gga aat gac ctt ggg gtc aca gtt caa gtg acc att gac cca gcg tcg Gly Asn Asp Leu Gly Val Thr Val Gln Val Thr Ile Asp Pro Ala Ser 115 120 125	500
act cct gcc ccc acc acg cct acc tcc act acg ttt aca gca cca gtc Thr Pro Ala Pro Thr Thr Pro Thr Ser Thr Thr Phe Thr Ala Pro Val 130 145	548
acc caa gaa gaa act agc agc tcc cca act ctg acc ggc cac cac ttg Thr Gln Glu Glu Thr Ser Ser Pro Thr Leu Thr Gly His His Leu  150 160	596
gac aac agg cac aag ctc ctg aag ctc agt gtc ctc ctg ccc ctc atc Asp Asn Arg His Lys Leu Leu Lys Leu Ser Val Leu Leu Pro Leu Ile 165 170 175	644
ttc acc ata ttg ctg ctg ctt ttg gtg gcc gcc tca ctc ttg gct tgg Phe Thr Ile Leu Leu Leu Leu Val Ala Ala Ser Leu Leu Ala Trp 180 185 190	692
agg atg atg aag tac cag cag aaa gca gcc ggg atg tcc cca gag cag Arg Met Met Lys Tyr Gln Gln Lys Ala Ala Gly Met Ser Pro Glu Gln 195 200 205	740
gta ctg cag ccc ctg gag ggc gac ctc tgc tat gca gac ctg acc ctg Val Leu Gln Pro Leu Glu Gly Asp Leu Cys Tyr Ala Asp Leu Thr Leu 210 225	788

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gcc cag gtt gac cag gtg gaa gtg gaa tat gtc acc atg gct tcc ttg Ala Gln Val Asp Gln Val Glu Val Glu Tyr Val Thr Met Ala Ser Leu 245 250 255	884
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cag gaa ccg acc tac tgc aac atg ggc cac ctc agt agc cac ctc ccc Gln Glu Pro Thr Tyr Cys Asn Met Gly His Leu Ser Ser His Leu Pro 275 280 285	980
ggc agg ggc cct gag gag ccc acg gaa tac agc acc atc agc agg cct Gly Arg Gly Pro Glu Glu Pro Thr Glu Tyr Ser Thr Ile Ser Arg Pro 290 295 300 305	1028
tagcctgcac tecaggetec ttettggace ecaggetgtg ageacactee tgeetcateg	1088
accgtctgcc ccctgctccc ctcatcagga ccaacccggg gactggtgcc tctgcctgat	1148
cagccagcat tgcccctage tctgggttgg gcttggggcc aagtctcagg gggcttctag	1208
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<210> 156 <211> 842 <212> DNA

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gaa Glu	gcc Ala 75	agc Ser	tgg Trp	gly ggg	agg Arg	gcc Ala 80	agc Ser	agc Ser	cgg Arg	cca Pro	gca Ala 85	gcc Ala	ccc Pro	act Thr	cct Pro	351
ccc Pro 90	atg Met	cca Pro	gcc Ala	aac Asn	gta Val 95	cag Gln	gcc Ala	gga Gly	tgg Trp	gaa Glu 100	cag Gln	tct Ser	gtg Val	agg Arg	ctt Leu 105	399
ttg Leu	tgc Cys	cac His	tcc Ser	tgg Trp 110	ctg Leu	cgc Arg	ttg Leu	gca Ala	gct Ala 115	ctg Leu	cat His	gtc Val	aca Thr	cat His 120	gag Glu	447
	tcc Ser		gtc	tcaa	aat	ggcc	cag (	gaat	ccag	ca t	gagc	tgtg	c ta	ggag	tcaa	503
gag	gttt	gcc	acga	ctgg	gc t	tggt	tcct	t gt	tcat	gagc	gag	cacg	tcc	ctca	gtctat	563
cca	tcta	gct	ggtg	acgt	tt c	ctga	acac	c ag	ggga	gacc	agg	ctct	gtt	ctag	gcacgg	623
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gca	tggc	cct	cato	acca	gc c	gcct	gcga	g tc	tgtg	ccag	agc	agat	tgg	ggtg	acaaca	743
gac	tgca	ctg	tgtg	gggt	ga g	gggc	agca	t gt	ggct	ggcc	ccc	aaat	gag	ggga	gatatg	803
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Thr Val Tyr Leu Phe Tyr Leu Leu Arg Ser Asn Ile Trp Leu Glu Met

WO 01/55437			P	CT/US01/02623
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acc agt aat tat t Thr Ser Asn Tyr I 40		cacagatct ctct	tteettg ettgtte	ttg 560
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ccaaactatt ttggg	aagt ccctctattt	ctctaggtct a	aagctagga ataag	agtca 680
ttctcatata atgta	ctgtc ccagaaaggg	cattatatta gi	tctgttttc acgct	gctga 740
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gag gtg cag ctg Glu Val Gln Leu 20	gtg gag tct ggc Val Glu Ser Gly 25	gga ggc ttg g Gly Gly Leu V 30	ta aag ccg ggg al Lys Pro Gly	ggg 153 Gly 35
tct ctt agg ctc Ser Leu Arg Leu				
tac atg aac tgg Tyr Met Asn Trp 55				
ggc cgc att aaa Gly Arg Ile Lys 70				
ccc gtg aaa ggc Pro Val Lys Gly 85		Ser Arg Asp A		

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		_			ggc Gly	_			-	_	-	_				251
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tat Tyr	gca Ala 80	gac Asp	tcc Ser	gtg Val	aag Lys	ggc Gly 85	cga Arg	ttc Phe	acc Thr	atc Ile	tcc Ser 90	aga <b>Arg</b>	gac Asp	aat Asn	tcc Ser	347
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gct Ala	gtg Val	tat Tyr	tat Tyr	tgt Cys 115	gcg Ala	aga Arg	gag Glu	ggt Gly	cgg Arg 120	tgg Trp	gta Val	cga Arg	tat Tyr	act Thr 125	acg Thr	443
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					gcc Ala											539
					agc Ser											587
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					ggc Gly											683
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	_		_	-	cca Pro 260	_		_		-			_		-	875
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					gtg Val											971

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230

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Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Val Gln Leu Arg Ser
275 280 285

gca aga ttg taa gga cagcetgtge teeetegete etteetetgg cattgeecet 919
Ala Arg Leu \*
290

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atg gta ctg aga ctg cct tgg tgg gga gtt ttg gcc tat ggg aat gat 226
Met Val Leu Arg Leu Pro Trp Trp Gly Val Leu Ala Tyr Gly Asn Asp 1 5 10
gtg ggt ttt ggt ttc tac tcc ttt ctc tgt tat cag ata aat cct cct
Val Gly Phe Gly Phe Tyr Ser Phe Leu Cys Tyr Gln Ile Asn Pro Pro

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Thr Cys Pro Ile Leu Trp Leu Trp Glu Val Leu Thr Val Gly Lys Ser
35 40 45

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Leu · Glu	Ala	Asn	Gly 175	Arg	Lys	Val	Arg	Gly 180	Gly	Leu	Pro	Leu	Val 185	Thr	
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agg gac Arg Asp															796
gcc atc Ala Ile 220	Pro														844
gcc tgg Ala Trp 235															892
ctg atg Leu Met															940
agc tac Ser Tyr															988
ctg gtg Leu Val		Ala													1036
gct gcc Ala Ala 300	Leu														1084
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ttc acc				Asp											1180
ctg tto Leu Phe			Glu					Arg							1228
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agagaca								•							
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wo	01/5	5437												F	CT/US01/0	2623
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tgc Cys	cag Gln 130	ctg Leu	cta Leu	aag Lys	atc Ile	atc Ile 135	gat Asp	tta Leu	ggt Gly	ggc Gly	tgc Cys 140	tta Leu	agt Ser	att Ile	act Thr	730
gat Asp 145	gtg Val	tcc Ser	tta Leu	cat His	gca Ala 150	tta Leu	gga Gly	aaa Lys	aac Asn	tgc Cys 155	cca Pro	ttt Phe	ttg Leu	cag Gln	tgt Cys 160	778
gtc Val	gac Asp	ttt Phe	tca Ser	gct Ala 165	act Thr	cag Gln	gta Val	tct Ser	gac Asp 170	agt Ser	ggt Gly	gtg Val	att Ile	gca Ala 175	ctt Leu	826
gtt Val	agt Ser	gga Gly	cct Pro 180	tgt Cys	gcg Ala	aag Lys	aaa Lys	tta Leu 185	gag Glu	gag Glu	att Ile	cat His	atg Met 190	gga Gly	cat His	874
tgt Cys	gta Val	aat Asn 195	ctg Leu	act Thr	gat Asp	Gly aaa	gct Ala 200	gtc Val	gaa Glu	gct Ala	gtc Val	ctt Leu 205	act Thr	tac Tyr	tgt Cys	922
cct Pro	caa Gln 210	Ile	cgt Arg	ata Ile	tta Leu	ctc Leu 215	Phe	cat His	gga Gly	tgc Cys	ccc Pro 220	ttg Leu	ata Ile	aca Thr	gat Asp	970
cat His 225	Ser	cga Arg	gaa Glu	gtg Val	ttg Leu 230	Glu	caa Gln	tta Leu	gta Val	ggc Gly 235	Pro	aac Asn	aaa Lys	cta Leu	aag Lys 240	1018
caa Gln	gtg Val	aca Thr	tgg Trp	act Thr 245	· Val	tat Tyr	tga *	tgc	tttt	ttg	aaga	tgat	ca a	tgct	aggaa	1072
agc	ttat	caa	aact	actt	tc c	cago	aaac	c at	ctat	ag <b>a</b> g	att	tgca	ttc	tact	taatgt	1132
taa	.cact	att	ttta	atta	itt t	tatt	gtct	t aa	ıgtta	taac	tct	caga	gaa	ttag	ctaagt	1192
ctt	ggta	tat	acat	ggtt	tg t	gctt	tact	c tt	aaac	atct	tta	aagt	gct	atta	ttctat	1252
ato	tgtt	gga	tgaç	gtcat	ta t	ttt	gaaa	at ga	taat	ccta	gca	tgaa	ctc	tgat	ctatgg	1312
tgt	tgga	attc	tgtt	tctt	aa a	taad	ettta	aa aa	attaa	ctgt	ttt	ccct	tga	gatt	tectte	1372
tcc	etate	gtag	gtat	ttga	agc t	att	ttct	ta ag	gttta	acctg	, taa	igtat	aaa	cctt	gggaga	1432
ato	ctaaç	gtaa	acat	attt	ct a	aaaq	gcata	ag ti	cacct	tcct	att	ttet	ggc	tctt	accttc	1492
ttg	gag	tatt	taaa	atgc	cca t	ttg	ccaaa	aa go	caga	cctga	a aca	atcaa	gcc	tggt	taattc	1552
nto	caaa	gaat	ttag	3333	att 9	gtti	tece	cg ga	aaatq	ggagt	ga(	ettat	tag	ccat	ttcagcg	1612
gta	atta	ggaa	taca	agag	get (	ttg	ccca	ge e	acat	ccant	c cca	attgi	nttt	taa	ggggact	1672
cct	ccc	aggt	aca	tttt	aag g	gcac	cggt	ag cı	nttc	cctc	c cta	aggca	aaat	tgc	atccnaa	1732
agg	gngg	taaa	aag	gggn	aat a	acng	gata	tc c	ctcn	3333	c tg	gtt				1777

<210> 164 <211> 1939 <212> DNA

PCT/US01/02623 WO 01/55437 <213> Homo sapiens <220> <221> CDS <222> (1)..(1704) <400> 164 atg gat tot ata otg att oot oca ott act aag agg ttg aaa atg ggo 48 Met Asp Ser Ile Leu Ile Pro Pro Leu Thr Lys Arg Leu Lys Met Gly aag toa ott tac etc tet gtg eeg cag ttt eet get tgt aac ace tac 96 Lys Ser Leu Tyr Leu Ser Val Pro Gln Phe Pro Ala Cys Asn Thr Tyr 20 age tge tee etg aac etc aga gat gee aat gag geg gat aca ggg acg 144 Ser Cys Ser Leu Asn Leu Arg Asp Ala Asn Glu Ala Asp Thr Gly Thr tac ttc ttt cag gtg gag aga ggt tat tac atg aaa tac agt tac gga 192 Tyr Phe Phe Gln Val Glu Arg Gly Tyr Tyr Met Lys Tyr Ser Tyr Gly 55 aat gag aag ttg ttc ttg cat gtg aca agg cct cct cta agt ctt gag 240 Asn Glu Lys Leu Phe Leu His Val Thr Arg Pro Pro Leu Ser Leu Glu ccc gca gtt cct gag aga aga acc ctg agg aac aga cgt tcc ctc gcg 288 Pro Ala Val Pro Glu Arg Arg Thr Leu Arg Asn Arg Arg Ser Leu Ala 90 ged etg gea eet eta acc eea gae atg etg etg etg etg eec etg 336 Ala Leu Ala Pro Leu Thr Pro Asp Met Leu Leu Leu Leu Pro Leu ctc tgg ggg agg gag agg gcg gaa gga cag aca agt aaa ctg ctg acg Leu Trp Gly Arg Glu Arg Ala Glu Gly Gln Thr Ser Lys Leu Leu Thr 115 atg cag agt tcc gtg acg gtg cag gaa ggc ctg tgt gtc cat gtg ccc 432 Met Gln Ser Ser Val Thr Val Gln Glu Gly Leu Cys Val His Val Pro 135 130 480 tgc tcc ttc tcc tac ccc tcg cat ggc tgg att tac cct ggc cca gta Cys Ser Phe Ser Tyr Pro Ser His Gly Trp Ile Tyr Pro Gly Pro Val gtt cat ggc tac tgg ttc cgg gaa ggg gcc aat aca gac cag gat gct 528 Val His Gly Tyr Trp Phe Arg Glu Gly Ala Asn Thr Asp Gln Asp Ala 170 cca gtg gcc aca aac aac cca gct cgg gca gtg tgg gag gag act cgg 576 Pro Val Ala Thr Asn Asn Pro Ala Arg Ala Val Trp Glu Glu Thr Arg 180 185 gac eqa tte cae etc ett ggg gac eca cat ace gag aat tge ace etg 624 Asp Arg Phe His Leu Leu Gly Asp Pro His Thr Glu Asn Cys Thr Leu 200

agc atc aga gat gcc aga aga agt gat gcg ggg aga tac ttc ttt cgt Ser Ile Arg Asp Ala Arg Arg Ser Asp Ala Gly Arg Tyr Phe Phe Arg

atg gag aaa gga agt ata aaa tgg aat tat aaa cat cac cgg ctc tct

210

672

WU	01/3	3431												-	-, -,	002,0202
Met 225	Glu	Lys	Gly	Ser	Ile 230	Lys	Trp	Asn	Tyr	Lys 235	His	His	Arg	Leu	Ser 240	
				gcc Ala 245												768
acc Thr	ctg Leu	gag Glu	tcc Ser 260	ggc Gly	tgc Cys	ccc Pro	cag Gln	aat Asn 265	ctg Leu	acc Thr	tgc Cys	tct Ser	gtg Val 270	ccc Pro	tgg Trp	816
gcc Ala	tgt Cys	gag Glu 275	cag Gln	gjå aaa	aca Thr	ccc Pro	cct Pro 280	atg Met	atc Ile	tcc Ser	tgg Trp	ata Ile 285	Gly ggg	acc Thr	tcc Ser	864
gtg Val	tcc Ser 290	ccc Pro	ctg Leu	gac Asp	ccc Pro	tcc Ser 295	acc Thr	acc Thr	cgc Arg	tcc Ser	tcg Ser 300	gtg Val	ctc Leu	acc Thr	ctc Leu	912
atc Ile 305	cca Pro	cag Gln	ccc Pro	cag Gln	gac Asp 310	cat His	ggc Gly	acc Thr	agc Ser	ctc Leu 315	acc Thr	tgt Cys	cag Gln	gtg Val	acc Thr 320	960
ttc Phe	cct Pro	Gly 999	gcc Ala	agc Ser 325	gtg Val	acc Thr	acg Thr	aac Asn	aag Lys 330	acc Thr	gtc Val	cat His	ctc Leu	aac Asn 335	gtg Val	1008
tcc Ser	tac Tyr	ccg Pro	cct Pro 340	cag Gln	aac Asn	ttg Leu	acc Thr	atg Met 345	act Thr	gtc Val	ttc Phe	caa Gln	gga Gly 350	gac Asp	ggc Gly	1056
aca Thr	gta Val	tcc Ser 355	Thr	gtc Val	ttg Leu	gga Gly	aat Asn 360	ggc	tca Ser	tct Ser	ctg Leu	tca Ser 365	ctc Leu	cca Pro	gag Glu	1104
				cgc Arg								Val				1152
	Pro			ctg Leu												1200
										Leu					ctg Leu	1248
									Ala						tct Ser	1296
_	_	_	Tyr	_				Leu	_	_			Thr		gga Gly	1344
		Gln					Gly					Ala			ttc Phe	1392
	Ser					Phe					Ser				aaa Lys 480	1440
tcg	gca	agg	r cca	. gca	gcg	ggc	gtg	gga	gat	acg	ggd	ata	gag	gat	gca	1488

Ser Ala Arg Pro Ala Ala Gly Val Gly Asp Thr Gly Ile Glu Asp Ala 485 490 495	
aac gct gtc agg ggt tca gcc tct cag ggg ccc ctg act gaa cct tggAsn Ala Val Arg Gly Ser Ala Ser Gln Gly Pro Leu Thr Glu Pro Trp500505	1536
gca gaa gac agt ccc cca gac cag cct ccc cca gct tct gcc cgc tcc Ala Glu Asp Ser Pro Pro Asp Gln Pro Pro Pro Ala Ser Ala Arg Ser 515 520 525	1584
tca gtg ggg gaa gga gag ctc cag tat gca tcc ctc agc ttc cag atg Ser Val Gly Glu Gly Glu Leu Gln Tyr Ala Ser Leu Ser Phe Gln Met 530 535 540	1632
gtg aag oot tgg gac tcg cgg gga cag gag gcc act gac acc gag tac Val Lys Pro Trp Asp Ser Arg Gly Gln Glu Ala Thr Asp Thr Glu Tyr 545 550 555 560	1680
tcg gag atc aag atc cac aga tga gaaactgcag agactcaccc tgattgaggg Ser Glu Ile Lys Ile His Arg * 565	1734
atcacagece etecaggeaa gggagaagte agaggetgat tettgtagaa ttaacagece	1794
tcaacgtgat gagctatgat aacactatga attatgtgca gagtgaaaag cacacaggct	1854
ttagagteaa agtateteaa acetgaatee acaetgtgee etceetttta ttttttaac	1914
taaaagacag acaaattcct acctc	1939

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<213> Homo sapiens

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WO 01/55437 PCT/US01/02623 ttt ggg ctt gcc ttg caa ttg atc ctc gat ttg aaa ctg aca act gtg 643 Phe Gly Leu Ala Leu Gln Leu Ile Leu Asp Leu Lys Leu Thr Thr Val

aac cag cga gaa agt gat gtg gca aga gtt gcc acg gct gaa gaa tat 691 Asn Gln Arg Glu Ser Asp Val Ala Arg Val Ala Thr Ala Glu Glu Tyr 25

tca aag aaa ggt ctg ctt gga cag gaa aca ctt cat gct gga tca cag 739 Ser Lys Lys Gly Leu Leu Gly Gln Glu Thr Leu His Ala Gly Ser Gln 40

aca aga atg cag att ctt atc tcc tga gaccc cttgaattcc accgcaagtg 791 Thr Arg Met Gln Ile Leu Ile Ser \*

g 792

<210> 166 <211> 797 <212> DNA <213> Homo sapiens <220> <221> CDS

<222> (206)..(418)

<400> 166

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ttattagtat gtgttccaaa attatgggaa attcctataa ttctatataa ctcagtgtac 180

attatcagta ataatcataa tigit atg tta aaa tta tig igt gcc gca gag 232 Met Leu Lys Leu Leu Cys Ala Ala Glu

gta aca aat gtc ctt ttc aac tgt gtt ttt gac tat ggc tgt cct aaa 280 Val Thr Asn Val Leu Phe Asn Cys Val Phe Asp Tyr Gly Cys Pro Lys 10 15 20

act tit tgt cat cca tgg aca att tit gtc tig tit tgg tcc tct tia 328 Thr Phe Cys His Pro Trp Thr Ile Phe Val Leu Phe Trp Ser Ser Leu 30

gaa ggt ggc ttt ata atc agc tac aaa act cta aca ggt gct ctt gaa 376 Glu Gly Gly Phe Ile Ile Ser Tyr Lys Thr Leu Thr Gly Ala Leu Glu 50

tgc agg ttt ctg ata act ttg gag att gtg aca tca gaa tag aggaaaa 425 Cys Arg Phe Leu Ile Thr Leu Glu Ile Val Thr Ser Glu \*

65 actttcagga ctcatggaga gctataaaat attcatgagt atcaagcaga acaggaatta 485 actgcatgga ctgaactgat ctttttgact ttttgcttaa aaagttgctg atctttttgt ttgcttttca gagccttaaa acttttcttt tgagctattg gcagctttta acaatttacg

atacttccat aaacaaaget, tgcagcctat ttgttgctct ttaactgact tctgccgaat 665
tcgcacacta ttcgctcgca ctccctactc atcggccctc cggcaatacc ccacccggcc 725
ccaccaatcc tgtgctcctc gatacctaga cccctactgg gcgcacctgc gttcgcctac 785
caccgagtgg cg 797

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<221> CDS

<222> (241)..(1050)

<400> 167 tgcctgtatg tctgaggctg ggtttgaagc ctccagcgtg tttggagtta atccccatta 60 ggttggactc cgcccctttc tcccaaaggt aaagcaaggt tttcaggcat cactgcaaag 120 ggcagctagt attcccatcc ttgtctaaca agctgtaagg agaagttgtt tctgagatct 180 qaqcctgaag agagggaaca agtcagtcag ccttcgtggt cagaagagaa acctgtgacc 240 atg agg agc agc ctg acc atg gtg gga acc ctc tgg gcc ttc ctg tcc 288 Met Arg Ser Ser Leu Thr Met Val Gly Thr Leu Trp Ala Phe Leu Ser ctt gtt act gct gtg acc agt tct acc agt tac ttc cta cct tac tgg 336 Leu Val Thr Ala Val Thr Ser Ser Thr Ser Tyr Phe Leu Pro Tyr Trp 384 ctc ttt gga tcc cag atg ggg aag cca gtg tca ttc agc aca ttc cgg Leu Phe Gly Ser Gln Met Gly Lys Pro Val Ser Phe Ser Thr Phe Arg 40 agg tgc aac tac cct gtg cgg gga gag gga cac agt ctg atc atg gtg 432 Arg Cys Asn Tyr Pro Val Arg Gly Glu Gly His Ser Leu Ile Met Val gaa gaa tgt ggg cgc tat gcc agc ttc aat gcc atc cca agc ctg gcc 480 Glu Glu Cys Gly Arg Tyr Ala Ser Phe Asn Ala Ile Pro Ser Leu Ala 528 tgg cag atg tgc aca gtg gtg aca ggt gcc ggc tgt gct ctg ctc Trp Gln Met Cys Thr Val Val Thr Gly Ala Gly Cys Ala Leu Leu Leu 85 ctg gtg gca cta gct gct gtc ctg ggt tgc tgc atg gag gag ctc atc 576 Leu Val Ala Leu Ala Ala Val Leu Gly Cys Cys Met Glu Glu Leu Ile 105 tee aga atg atg gga egt tge atg gga gea geg eag ttt gtt gga ggg 624 Ser Arg Met Met Gly Arg Cys Met Gly Ala Ala Gln Phe Val Gly Gly 120

ctg ctg ata agc tca ggc tgt gcc tta tac cct tta gga tgg aat agc Leu Leu Ile Ser Ser Gly Cys Ala Leu Tyr Pro Leu Gly Trp Asn Ser

130 135 140 ccg gag ata atg caa aca tgt ggg aat gtc tcc aat caa ttt cag tta 720 Pro Glu Ile Met Gln Thr Cys Gly Asn Val Ser Asn Gln Phe Gln Leu 150 768 ggt acc tgt cgg ctt ggc tgg gcc tat tac tgt gct gga ggt gga aca Gly Thr Cys Arg Leu Gly Trp Ala Tyr Tyr Cys Ala Gly Gly Gly Thr 165 cct gca gcc atg ttg atc tgc ccc tgg ctc tct tgc ttt gct gga aga 816 Pro Ala Ala Met Leu Ile Cys Pro Trp Leu Ser Cys Phe Ala Gly Arg 185 aac ccc cag cct gtc ata ttg ggg ggg aag cac cat gag.gaa aac cac Asn Pro Gln Pro Val Ile Leu Gly Gly Lys His His Glu Glu Asn His 200 195 ttc tta tgc tat gga gct tgg cca ttg ccc tca acc ctt gag ctt cga 912 Phe Leu Cys Tyr Gly Ala Trp Pro Leu Pro Ser Thr Leu Glu Leu Arg aaa gaa gac cgg ggg ggg cgg gca aca ggg aag caa gtg acc ccc caa 960 Lys Glu Asp Arg Gly Gly Arg Ala Thr Gly Lys Gln Val Thr Pro Gln 230 cca ctt aga ttc cat gtc tct act tgg atg tct agt aga ctt gac aga 1008 Pro Leu Arg Phe His Val Ser Thr Trp Met Ser Ser Arg Leu Asp Arg 245 gtg tac ata tcc ata acc aag atc caa atc ttc caa tcc taa acccat 1056 Val Tyr Ile Ser Ile Thr Lys Ile Gln Ile Phe Gln Ser \* 260 265

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<213> Homo sapiens

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<221> CDS
<222> (73)..(858)

<220>
<221> misc\_feature
<222> (1)...(958)
<223> n = a,t,c or g

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taacgcgatc tgagcctgaa gagagggaac aagtcagtca gccttcgcgg acattttatt

tatcctgtga cc atg aag agc ctg acc gtg gtg gga acc ctc tgg 108

Met Lys Ser Ser Leu Thr Val Val Gly Thr Leu Trp

1 5 10

60

ged ttd ctg ted ctt gtt act get gtg acc agt tet acc agt tac ttd 156
Ala Phe Leu Ser Leu Val Thr Ala Val Thr Ser Ser Thr Ser Tyr Phe
15 20 25

cta cct tac tgg ctc ttt gga tcc cag atg ggg aag cca gtg tca ttc 204

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Leu Pro Tyr Trp Leu Phe Gly Ser Gln Met Gly Lys Pro Val Ser Phe 30 40	
age aca tte egg agg tge aac tae eet gtg egg gga gag gga eac agt Ser Thr Phe Arg Arg Cys Asn Tyr Pro Val Arg Gly Glu Gly His Ser 45 50 55 60	252
ctg atc atg gtg gaa gaa tgt ggg cgc tat gcc agc ttc aat gcc atc Leu Ile Met Val Glu Glu Cys Gly Arg Tyr Ala Ser Phe Asn Ala Ile 65 70 75	300
cca agc ctg gcc tgg cag atg tgc aca gtg gtg aca ggt gcc ggc tgt Pro Ser Leu Ala Trp Gln Met Cys Thr Val Val Thr Gly Ala Gly Cys 80 85 90	348
gct ctg ctg ctc ctg gag tca cta gct gct gtc ctg ggt tgc tgc atg Ala Leu Leu Leu Glu Ser Leu Ala Ala Val Leu Gly Cys Cys Met 95 100 105	396
gag gag ctc atc tcc aga atg atg gga cgt tgc atg gga gca gcg cag Glu Glu Leu Ile Ser Arg Met Met Gly Arg Cys Met Gly Ala Ala Gln 110 115 120	444
ttt gtt gga ggt cca atg cag ccc ttc tgt gaa gcc ttc cct gat cta Phe Val Gly Gly Pro Met Gln Pro Phe Cys Glu Ala Phe Pro Asp Leu 125 130 135 140	492
ctt ttg aca tct tta gca gat atg aac gat cct gta act cca aga gga Leu Leu Thr Ser Leu Ala Asp Met Asn Asp Pro Val Thr Pro Arg Gly 145 150 155	540
ata tgg ggt aga atg aat ggc ggg ggc tgg ggg ggt ggg ctg ctg ata Ile Trp Gly Arg Met Asn Gly Gly Gly Trp Gly Gly Gly Leu Leu Ile 160 165 170	588
age tea gge tgt gee tta tae eet tta gga tgg aat age eeg gag ata Ser Ser Gly Cys Ala Leu Tyr Pro Leu Gly Trp Asn Ser Pro Glu Ile 175 180 185	636
atg caa aca tgt ggg aat gtc tcc aat caa ttt cag tta ggt acc tgt Met Gln Thr Cys Gly Asn Val Ser Asn Gln Phe Gln Leu Gly Thr Cys 190 200	684
cgg ctt ggc tgg gcc tat tac tgt gct gga ggt gga gca gct gca gcc Arg Leu Gly Trp Ala Tyr Tyr Cys Ala Gly Gly Gly Ala Ala Ala Ala 205 210 215 220	732
atg ttg atc tgc acc tgg ctc tct tgc ttt gct gga aga aac ccc aag Met Leu Ile Cys Thr Trp Leu Ser Cys Phe Ala Gly Arg Asn Pro Lys 225 230 235	780
cct gtc ata ttg gtg gag agc atc atg agg aat acc aat tct tat gct Pro Val Ile Leu Val Glu Ser Ile Met Arg Asn Thr Asn Ser Tyr Ala 240 245 250	828
atg gag ctt gac cat tgc ctc aaa cct tga g ctttgaaaga agattggaga Met Glu Leu Asp His Cys Leu Lys Pro * 255 260	879
gggttgggaa nggggaagga gggagccctg aaaaagaagg tacntagggt ttaaggccat	939
tttntcaacc tgacttttt	958

<210> 169 <211> 1906 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (108)..(1748) <400> 169 aegectgaeg taeeggteeg gaatteeegg gtegaegatt tegteaggge tqqaaqqtee tggcctggga tgaagagggg actgcctaag gctggggtgg ctccaag atg ccg gca 116 Met Pro Ala tgg gaa act ggg ggt ttc ctg gta act gga ctc cta gca aac tcc caa 164 Trp Glu Thr Gly Gly Phe Leu Val Thr Gly Leu Leu Ala Asn Ser Gln gga ttc agg atg tcg ctg ctg agc ctg ccc tgg ctg ggc ctc aga ccg Gly Phe Arg Met Ser Leu Leu Ser Leu Pro Trp Leu Gly Leu Arg Pro gtg gca acg tcc cca tgg cta ctc ctg ctg ctg gtt gtg ggc tcc tgg 260 Val Ala Thr Ser Pro Trp Leu Leu Leu Leu Val Val Gly Ser Trp 45 cta ctc gcc cgc atc ctg gct tgg acc tat gcc ttc tat aac aac tgc 308 Leu Leu Ala Arg Ile Leu Ala Trp Thr Tyr Ala Phe Tyr Asn Asn Cys 55 60 cgc cgg ctc cag tgt ttc cca cag ccc cca aaa cgg aac tgg ttt tgg 356 Arg Arg Leu Gln Cys Phe Pro Gln Pro Pro Lys Arg Asn Trp Phe Trp ggt cac ctg ggc ctg atc act cct aca gag gag ggc ttg aag aac tcg 404 Gly His Leu Gly Leu Ile Thr Pro Thr Glu Glu Gly Leu Lys Asn Ser 85 acc cag atg teg gee acc tat tee cag gge ttt acg ata tgg etg ggt 452 Thr Gln Met Ser Ala Thr Tyr Ser Gln Gly Phe Thr Ile Trp Leu Gly 105 110 ecc ate ate ecc tte ate gtt tta tge eac ect gae acc ate egg tet 500 Pro Ile Ile Pro Phe Ile Val Leu Cys His Pro Asp Thr Ile Arg Ser 125 atc acc aat gcc tca gct gcc att gca ccc aag gat aat ctc ttc atc 548 Ile Thr Asn Ala Ser Ala Ala Ile Ala Pro Lys Asp Asn Leu Phe Ile agg ttc ctg aag ccc tgg ctg gga gaa ggg ata ctg ctg agt ggc ggt 596 Arg Phe Leu Lys Pro Trp Leu Gly Glu Gly Ile Leu Leu Ser Gly Gly 155 gac aag tgg agc cgc cac cgt cgg atg ctg acg ccc gcc ttc cat ttc 644 Asp Lys Trp Ser Arg His Arg Arg Met Leu Thr Pro Ala Phe His Phe 165 170 aac atc ctg aag tcc tat ata acg atc ttc aac aag agt gca aac atc 692 Asn Ile Leu Lys Ser Tyr Ile Thr Ile Phe Asn Lys Ser Ala Asn Ile

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180					185			•		190					195	
_		-	_		_			-				agc Ser	_	_		740
												agt Ser				788
												ccc Pro 240				836
	-			_			_	_				aaa Lys	_	_		884
			-		_	_		_				tcc Ser		_		932
	-				_	_	_	_			_	ttc Phe	-		-	980
												ggt Gly				1028
			-		_	-		_		_	_	ttc Phe 320				1076
												tca Ser				1124
	-	_	-	-				_				cat His	_		-	1172
_	-					-	_					agg Arg			_	1220
			_	_	_	-						ctg Leu	-	_	_	1268
												ctg Leu 400				1316
												cca Pro				1364
												gat Asp				1412
						_			_			gjà aaa	_			1460

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440 445 450	
Asn Pro Thr Val Trp Pro Asp Pro Glu Val Tyr Asp Pro Phe Arg Phe 455 460 465	1508
gac cca gag aac agc aag ggg agg tca cct ctg gct ttt att cct ttc Asp Pro Glu Asn Ser Lys Gly Arg Ser Pro Leu Ala Phe Ile Pro Phe 470 475 480	1556
tcc gca ggg ccc agg aac tgc atc ggg cag gcg ttc gcc atg gcg gag Ser Ala Gly Pro Arg Asn Cys Ile Gly Gln Ala Phe Ala Met Ala Glu 485 490 495	1604
atg aaa gtg gtc ctg gcg ttg atg ctg ctg cac ttc cgg ttc ctg cca Met Lys Val Val Leu Ala Leu Met Leu Leu His Phe Arg Phe Leu Pro 500 505 510 515	1652
gac cac act gag ccc cgc agg aag ctg gaa ttg atc atg cgc gcc gag Asp His Thr Glu Pro Arg Arg Lys Leu Glu Leu Ile Met Arg Ala Glu 520 525 530	1700
ggc ggg ctt tgg ctg cgg gtg gag ccc ctg aat gta agc ttg cag tga Gly Gly Leu Trp Leu Arg Val Glu Pro Leu Asn Val Ser Leu Gln * 535 540 545	1748
etttetgace catecacetg tttttttgca gattgtcatg aataaaaegg tgctgtcaaa	1808
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tggcctggga tgaagagggg actgcctaag gctggggtgg ctccaag atg ccg gca Met Pro Ala 1	116
tgg gaa act ggg ggt ttc ctg gta act gga ctc cta gca aac tcc caa Trp Glu Thr Gly Gly Phe Leu Val Thr Gly Leu Leu Ala Asn Ser Gln 5 10 15	164

Gly Phe Arg Met Ser Leu Leu Ser Leu Pro Trp Leu Gly Leu Arg Pro

gtg gca acg tcc cca tgg cta ctc ctg ctg ctg gtt gtg ggc tcc tgg

Val Ala Thr Ser Pro Trp Leu Leu Leu Leu Val Val Gly Ser Trp

cta ctc gcc cgc atc ctg gct tgg acc tat gcc ttc tat aac aac tgc

WO	01/5	5437												-	01.00	•
Leu	Leu	Ala	Arg 55	Ile	Leu	Ala	Trp	Thr 60	Tyr	Ala	Phe	Tyr	Asn 65	Asn	Cys	
cgc Arg	cgg Arg	ctc Leu 70	cag Gln	tgt Cys	ttc Phe	cca Pro	cag Gln 75	ccc Pro	cca Pro	aaa Lys	cgg Arg	aac Asn 80	tgg Trp	ttt Phe	tgg Trp	356
ggt Gly	cac His 85	ctg Leu	ggc Gly	ctg Leu	atc Ile	act Thr 90	cct Pro	aca Thr	gag Glu	gag Glu	ggc Gly 95	ttg Leu	aag Lys	aac Asn	tcg Ser	404
acc Thr 100	cag Gln	atg Met	tcg Ser	gcc Ala	acc Thr 105	tat Tyr	tcc Ser	cag Gln	ggc Gly	ttt Phe 110	acg Thr	ata Ile	tgg Trp	ctg Leu	ggt Gly 115	452
ccc Pro	atc Ile	atc Ile	ccc Pro	ttc Phe 120	atc Ile	gtt Val	tta Leu	tgc Cys	cac His 125	cct Pro	gac Asp	acc Thr	atc Ile	cgg Arg 130	tct Ser	500
atc Ile	acc Thr	aat Asn	gcc Ala 135	tca Ser	gct Ala	gcc Ala	att Ile	gca Ala 140	ccc Pro	aag Lys	gat Asp	aat Asn	ctc Leu 145	ttc Phe	atc Ile	548
agg Arg	ttc Phe	ctg Leu 150	Lys	ccc Pro	tgg Trp	ctg Leu	gga Gly 155	gaa Glu	Gly	ata Ile	ctg Leu	ctg Leu 160	agt Ser	ggc Gly	ggt Gly	596
gac Asp	aag Lys 165	tgg Trp	agc Ser	cgc Arg	cac His	cgt Arg 170	cgg Arg	atg Met	ctg Leu	acg Thr	ccc Pro 175	gcc Ala	ttc Phe	cat His	ttc Phe	644
aac Asn 180	atc Ile	ctg Leu	aag Lys	tcc Ser	tat Tyr 185	Ile	acg Thr	atc Ile	ttc Phe	aac Asn 190	Lys	agt Ser	gca Ala	aac Asn	atc Ile 195	692
atg Met	ctt Leu	gac Asp	aag Lys	tgg Trp 200	Gln	cac His	ctg Leu	gcc Ala	tca Ser 205	Glu	ggc	agc Ser	agt Ser	tgt Cys 210	Leu	740
gac Asp	atg Met	ttt Phe	gag Glu 215	His	atc Ile	agc Ser	Leu	atg Met 220	Thr	ttg Leu	gac Asp	agt Ser	cta Leu 225	GIN	aaa Lys	788
tgc Cys	atc Ile	tto Phe 230	Ser	ttt Phe	Asp	Ser	His	Cys	Glr	Glu	Arc	pro 240	Ser	gaa Glu	tat Tyr	836
att Ile	gcc Ala 245	Thi	ato Ile	ttg Lev	g gag 1 Glu	cto Leu 250	Sex	gcc Ala	ctt Lei	gta Val	gag Glu 259	ı Lys	aga Arg	ago Ser	cag Gln	884
cat His 260	: Ile	c cto	cag ıGlr	cac His	atg Met 265	Asp	ttt Phe	t cto	g tat ı Tyr	tac Tyr 270	Lei	tco Ser	cat His	gac Asp	999 Gly 275	932
cgg Arg	j ėgo į Arg	tto Phe	c cac e His	agg Arg 280	g Ala	tgo Cys	cgc Arg	ctq Let	g gtg 1 Val 289	His	gad S Ası	tto Phe	aca Thi	gac Asp 290	gct Ala	980
gto Val	ato L Ile	cgg Arg	g gag g Glv 295	a Arg	g egt	cgo g Arg	aco Thi	c cto Let 300	ı Pro	c act	caq c Gl	g ggt n Gly	: att / Ile 309	As <u>r</u>	gat Asp	1028
ttt	tte	c aa	a gad	aaa	a gc	aag	g tc	c aaq	g act	ttg	g ga	t tto	att	; gat	gtg	1076

***	, 01,0													_		
Phe	Phe	Lys 310	Asp	Lys	Ala	Lys	Ser 315	Lys	Thr	Leu	Asp	Phe 320	Ile	Asp	Val	
	_	-	-	_	-	-	-	gly ggg	_	_			_			1124
								atg Met								1172
								aag Lys								1220
			_			_	-	ggc Gly 380					_			1268
								gag Glu								1316
								aaa Lys								1364
_	_	_			-		_	tgc Cys		-		_	-			1412
			_					cga Arg	_	_		_	-		-	1460
		-		-	-			aaa Lys 460				-			-	1508
			-					act Thr			_	_			-	1556
	-	Pro	Phe	Arg	Phe	-	Pro	gag Glu	Asn	Ser	_	Gly				1604
_	Āla						_	gly ggg				_				1652
								gtg Val								1700
								act Thr 540								1748
								ctt Leu								1796
aat	gta	ggc	ttg	cag	tga	ctt	tot (	gacc	catc	ca c	ctgt	tttt	t tg	caga	ttgt	1850

Asn Val Gly Leu Gln \* 565

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ctg tcc tgg ctg ggc ctc ggg cag gtg gca gca ttc ccg tgg c Leu Ser Trp Leu Gly Leu Gly Gln Val Ala Ala Phe Pro Trp L 10 15	etg ctc 162 Leu Leu 20
ctg ctg ctg gct ggg gcc tcc cgg ctc ctg gcc ggc ttc ctg g Leu Leu Leu Ala Gly Ala Ser Arg Leu Leu Ala Gly Phe Leu A 25 30 35	cc tgg 210 la Trp
acc tat gcc ttc tat gac aac tgc cgc cgc ctt cag tac ttt c Thr Tyr Ala Phe Tyr Asp Asn Cys Arg Arg Leu Gln Tyr Phe P 40 45 50	ca caa 258 Pro Gln
CCC CCa aaa cag aaa tgg ttt tgg ggt caa cca gga cct cct g Pro Pro Lys Gln Lys Trp Phe Trp Gly Gln Pro Gly Pro Pro A 55 60 65	gct att 306 Ala Ile
gcg ccc aag gat gat ctc tcc atc agg ttc ctg aag ccc tgg c Ala Pro Lys Asp Asp Leu Ser Ile Arg Phe Leu Lys Pro Trp L 70 75 80	etg gga 354 Leu Gly 85
gaa ggg ata ctg ctg agt ggc ggt gac aag tgg agc cgc cac c Glu Gly Ile Leu Leu Ser Gly Gly Asp Lys Trp Ser Arg His A 90 95	cgt cgg 402 Arg Arg L00
atg ctg acg ccc gcc ttc cat ttc aac atc ctg aaa ccc tat a Met Leu Thr Pro Ala Phe His Phe Asn Ile Leu Lys Pro Tyr I 105 110 115	ata aag 450 Ile Lys
atc ttc aac agg agt gtg aac atc atg cac gac aag tgg cag c Ile Phe Asn Arg Ser Val Asn Ile Met His Asp Lys Trp Gln H 120 125 130	cac ctg 498 His Leu
gcc tca gag ggc agc agt cgt ctg gac atg ttt gag cac atc a Ala Ser Glu Gly Ser Ser Arg Leu Asp Met Phe Glu His Ile S 135 140 145	
atg acc ttg gac agt ctg cag aaa tgc atc ttc agc ttt gac a Met Thr Leu Asp Ser Leu Gln Lys Cys Ile Phe Ser Phe Asp S 150 155 160	agc cat 594 Ser His 165

W	) 01/5	5437												I	PCT/US	S01/02623
tgt	cag	gag	agg	ccc	agt	gaa	tat	att	gct	acc	atc	ttg	gag	ctc	agt	642
Cys	Gln	Glu	Arg	Pro	Ser	Glu	Tyr	Ile	Ala	Thr	Ile	Leu	Glu	Leu	Ser	

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tgt Cys	cag Gln	gag Glu	agg Arg	ccc Pro 170	agt Ser	gaa Glu	tat Tyr	att Ile	gct Ala 175	acc Thr	atc Ile	ttg Leu	gag Glu	ctc Leu 180	agt Ser	642
gcc Ala	ctt Leu	gta Val	gaa Glu 185	aaa Lys	aga Arg	aac Asn	cag Gln	cat His 190	atc Ile	ctc Leu	cag Gln	cac His	atg Met 195	gac Asp	ttt Phe	690
ctg Leu	tat Tyr	tac Tyr 200	ctc Leu	tcc Ser	cat His	gac Asp	999 Gly 205	tgg Trp	cgc Arg	ttc Phe	cgc Arg	agg Arg 210	gcc Ala	tgc Cys	cgc Arg	738
ctg Leu	gtg Val 215	cac His	gac Asp	ttc Phe	aca Thr	gat Asp 220	gcc Ala	gtc Val	atc Ile	cag Gln	gag Glu 225	cgg Arg	cgc Arg	cat His	acc Thr	786
ctt Leu 230	ccc Pro	act Thr	cag Gln	ggc Gly	cat His 235	gac Asp	acc Thr	aca Thr	gcc Ala	agt Ser 240	ggt Gly	ctc Leu	tcc Ser	tgg Trp	gtc Val 245	834
ctg Leu	tac Tyr	aac Asn	ctc Leu	gcg Ala 250	agg Arg	cac His	cca Pro	gaa Glu	tac Tyr 255	cag Gln	gag Glu	cac His	tgc Cys	cgg Arg 260	cag Gln	882
gag Glu	gtg Val	caa Gln	gag Glu 265	ctt Leu	ctg Leu	aag Lys	gac Asp	cgc Arg 270	gat Asp	cct Pro	aaa Lys	gag Glu	att Ile 275	gaa Glu	tgg Trp	930
gac Asp	gac Asp	ctg Leu 280	gcc Ala	cag Gln	ctg Leu	ccc Pro	ttc Phe 285	ctg Leu	acc Thr	atg Met	tgc Cys	gtg Val 290	aag Lys	gag Glu	agc Ser	978
ctg Leu	agg Arg 295	tta Leú	cat His	ccc Pro	cca Pro	gct Ala 300	ccc Pro	ttc Phe	atc Ile	tcc Ser	cga Arg 305	tgc Cys	tgc Cys	acc Thr	cag Gln	1026
gac Asp 310	att Ile	gtt Val	ctc Leu	cca Pro	gat Asp 315	ggc Gly	cga Arg	gtc Val	atc Ile	ccc Pro 320	aaa Lys	ggc Gly	att Ile	acc Thr	tgc Cys 325	1074
ctc Leu	atc Ile	gat Asp	att Ile	ata Ile 330	gjå aaa	gtc Val	cat His	cac His	aac Asn 335	cca Pro	act Thr	gtg Val	tgg Trp	ccg Pro 340	gat Asp	1122
cct Pro	gag Glu	gtc Val	tac Tyr 345	gac Asp	ccc Pro	ttc Phe	cgc Arg	ttt Phe 350	gac Asp	cca Pro	gag Glu	aac Asn	agc Ser 355	aag Lys	GJ A aaa	1170
agg Arg	tca Ser	cct Pro 360	ctg Leu	gct Ala	ttt Phe	att Ile	cct Pro 365	ttc Phe	tcc Ser	gca Ala	gly ggg	ccc Pro 370	agg Arg	aac Asn	tgc Cys	1218
atc Ile	999 Gly 375	cag Gln	gcg Ala	ttc Phe	gcc Ala	atg Met 380	gcg Ala	gag Glu	atg Met	aaa Lys	gtg Val 385	gtc Val	ctg Leu	gcg Ala	ttg Leu	1266
atg Met 390	ctg Leu	ctg Leu	cac His	ttc Phe	cgg Arg 395	ttc Phe	ctg Leu	cca Pro	gac Asp	cac His 400	act Thr	gag Glu	ccc Pro	cgc Arg	agg Arg 405	1314
aag Lys	ctg Leu	gaa Glu	ttg Leu	atc Ile 410	atg Met	cgc Arg	gcc Ala	gag Glu	ggc Gly 415	gjå aaa	ctt Leu	tgg Trp	ctg Leu	cgg Arg 420	gtg Val	1362

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gag ccc ctg aat gta agc ttg cag tga ctttc tgacccatcc acctgttttt Glu Pro Leu Asn Val Ser Leu Gln *	1414
425 430	
ttgcagattg tcatgaataa aacggtgctg tcaaaaaaaa aaaagggggg gccctttaaa	1474
gggatcaaag tttaataccc ggggcgggga agggtaaatc tttttatagg gggccccaaa	1534
attaaatctc ggg	1547

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<220>

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WO 01/55437 Tyr Thr Gly	Sar Lau V	/al Asn	Glv Ara	Tle Tle	Asp Thr	Ser	-		,2020
65	Set Dea v	70	0 <u>-</u> 73	220 220	75				
aga gac cct	ctg gtt a	ata gaa	ctt ggc	caa aag	cag gtg	att	cca	ggt Gly	1066
Arg Asp Pro	Leu Val I	85	ren Già	90	GIII VAI	. 116	110	95	
ctg gag cag	agt ctt o	ctc gac	atg tgt	gtg gga	gag aag	cga	agg	gca	1114
Leu Glu Glr	Ser Leu I 100	Leu Asp	Met Cys	Val Gly 105	Glu Lys	Arg	Arg 110	Ala	
atc att cct	tct cac t	ttg gcc	tat gga	aaa cgg	gga ttt	cca	cca	tct	1162
Ile Ile Pro	Ser His I	Leu Ala	Tyr Gly	Lys Arg	Gly Phe	Pro 125	Pro	Ser	
gtc cca gcg	gat gca g	ata ata	cag tat	gac gtg	gag ct	, att	gca	cta	1210
Val Pro Ala	Asp Ala	Val Val	Gln Tyr	Asp Val	Glu Let	lle	Ala	Leu	
ate ega ge		taa cta		r ata aaa	ggc at	: ttq	cct	ctg	1258
Ile Arg Ala	Asn Tyr	Trp Leu 150	Lys Let	Val Lys	Gly Il	Leu	Pro	Leu	
145				act aca		- taa	αt a	tca	1306
gta ggg ate Val Gly Me	: Ala Met '	Val Pro	Thr Pro	Pro Gly	Pro Hi	Trp	Val	Ser 175	
160		165		170		<b>-</b>			1359
cct ata ca Pro Ile Gl			ac ccaa	agtete e	aaaaaga	ag ct	caag	gaag	1337
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									120
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gtegggaeee									300
cgggagggg	agggagag	, aaaa	arcase a	gactgggc	a dcadco	tate	acta	raccata	360
ccccaggco	ccctcagct	tt tgagg	gegetg c	tcgcccag	g tggggg	leget	gggc	ggcggc	420
ccccaggcc	ccctcagct	tt tgagg	gegetg c	tcgcccag	g tggggg	leget	gggc	ggcggc	

teggacecea tetteaeget ggegeeeeeg etgeattgee actaegggge etteeeeeet

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ctag	cage	ca g	cgcc	gcca	g cc	gtgt	cgcc	acc	agta	ccg	accc	ctcg	tg c	agcg	gcttc	660
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gaca	agatt	tg g	ccat	.cgcg	g ga	ttgt	gctg	ctg	acct	tgg	ggct	ggtg	igg c	ccct	gtgga	900
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ttg Leu	ggc Gly	ttt Phe	ctg Leu 10	ctt Leu	gcc Ala	ggt Gly	gtt Val	gac Asp 15	ctg Leu	ggt Gly	gtc Val	tac Tyr	ctg Leu 20	atg Met	cgc Arg	1002
ctg Leu	gag Glu	ctg Leu 25	tgc Cys	gac Asp	cca Pro	acc Thr	cag Gln 30	agg Arg	ctt Leu	cgg Arg	gtg Val	gcc Ala 35	ctg Leu	gca Ala	glà aaa	1050
gag Glu	ttg Leu 40	gtg Val	Gly ggg	gtg Val	gga Gly	999 Gly 45	cac His	ttc Phe	ctg Leu	ttc Phe	ctg Leu 50	ggc	ctg Leu	gcc Ala	ctt Leu	1098
gtc Val 55	tct Ser	aag Lys	gat Asp	tgg Trp	cga Arg 60	ttc Phe	cta Leu	cag Gln	cga Arg	atg Met 65	atc Ile	acc Thr	gct Ala	ccc Pro	tgc Cys 70	1146
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cgg Arg	tgg Trp	ctg Leu	ata Ile 90	gtg Val	aag Lys	cgg Arg	cag Gln	att Ile 95	gag Glu	gag Glu	gct Ala	cag Gln	tct Ser 100	gtg Val	ctg Leu	1242
agg Arg	atc Ile	ctg Leu 105	gct Ala	gag Glu	cga Arg	aac Asn	cgg Arg 110	ccc Pro	cat His	ggg Gly	cag Gln	atg Met 115	ctg Leu	gly aaa	gag Glu	1290
						cag Gln 125										1338
gca Ala 135	Thr	tcc Ser	tcc Ser	ttt Phe	tcc Ser 140	ttt Phe	gct Ala	tcc Ser	ctc Leu	ctc Leu 145	aac Asn	tac Tyr	cgc Arg	aac Asn	atc Ile 150	1386
						ctg Leu										1434
				Tyr		cct Pro										1482
			Cys			ctg Leu							Leu			1530

wo	01/5	5437												I	CT/US01	/02623
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ctt Leu 215	ctc Leu	tcc Ser	atg Met	acc Thr	ctt Leu 220	acc Thr	ggc	att Ile	gct Ala	tcc Ser 225	ctg Leu	gtc Val	ctg Leu	ctg Leu	ggc Gly 230	1626
ctg Leu	tgg Trp	gat Asp	tat Tyr	ctg Leu 235	aac Asn	gag Glu	gct Ala	gcc Ala	atc Ile 240	acc Thr	act Thr	ttc Phe	tct Ser	gtc Val 245	ctt Leu	1674
Gly 999	ctc Leu	ttc Phe	tcc Ser 250	tcc Ser	caa Gln	gct Ala	gcc Ala	gcc Ala 255	atc Ile	ctc Leu	agc Ser	acc Thr	ctc Leu 260	ctt Leu	gct Ala	1722
gct Ala	gag Glu	gtc Val 265	atc Ile	ccc Pro	acc Thr	act Thr	gtc Val 270	cgg Arg	ggc Gly	cgt Arg	ggc Gly	ctg Leu 275	ggc Gly	ctg Leu	atc Ile	1770
atg Met	gct Ala 280	Leu	Gly 333	gcg Ala	ctt Leu	gga Gly 285	gga Gly	ctg Leu	agc Ser	ggc Gly	ccg Pro 290	gcc Ala	cag Gln	cgc Arg	ctc Leu	1818
cac His 295	Met	ggc Gly	cat His	gga Gly	gcc Ala 300	ttc Phe	ctg Leu	cag Gln	cac His	gtg Val 305	gtg Val	ctg Leu	gcg Ala	gcc Ala	tgc Cys 310	1866
gcc Ala	ctc Leu	ctc Leu	tgc Cys	att Ile 315	ctc Leu	agc Ser	att Ile	atg Met	ctg Leu 320	Leu	ccg Pro	gag Glu	acc Thr	aag Lys 325	Arg	1914
aag Lys	ctc Leu	ctg Leu	ccc Pro	Glu	gtg Val	ctc Leu	cgg Arg	gac Asp 335	Gly	gag Glu	ctg Leu	tgt Cys	cgc Arg 340	Arg	cct Pro	1962
t co Ser	ctg Leu	ctg Lev 345	ı Arg	cag Gln	cca Pro	ccc Pro	cct Pro	Thr	cgc Arg	tgt Cys	gac Asp	cac His	Val	ccg Pro	ctg Leu	2010
		Thr		aac Asn			Leu		gcg	gc c	tctg	agta	.c cc	tggc	ggga	2062
ggo	tggc	cca	caca	ıgaaa	ıgg t	.ggca	agaa	g at	.cggg	aaga	ctg	agta	ggg	aagg	cagggc	2122
tgo	eccaç	gaag	tctc	agag	ıgc a	ccto	acgo	c ag	ccat	cgcg	gag	agct	cag	aggg	ccgtcc	2182
cca	accct	gcc	tcct	ccct	gc t	gctt	tgca	t to	actt	cctt	ggo	caga	gtc	aggg	gacagg	2242
gag	gagag	gete	caca	ctgt	aa c	cact	gggt	c tg	ggct	ccat	cct	gcgc	:cca	aaga	catcca	2302
cco	cagao	cctc	atta	tttc	ett g	ctct	atca	t to	tgtt	tcaa	taa	agac	att	tgga	ataaac	2362
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30

Ala Phe Leu Phe Thr Pro His His Val Leu Glu Arg Tyr Arg Tyr Tyr

WO 01/55437 PCT/US01/02	623
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aat tag tagaagaatt aaaattcaat ootaagtotg totgaccoca aagcocatga Asn *	433
atactettaa eteetatget gtaaatataa aaagaetgaa egggggeeag aegtggtgge	493
tcatgcctgt aatcccagca ctttgggagg atggtttgag cccaggagtt caagaccagc	553
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acctcaatta totoatotat aaaaggcago tagatottaa otoactgggt totogtgagg	240
attaaatgag atagtgcccc taaggtttct ggt atg aag gag gca ctc ctt aaa Met Lys Glu Ala Leu Leu Lys 1 5	294
tgt tcg aga ctt gcc aga ggg ctt ctt ctc tgt ctg gac tgt gct aat Cys Ser Arg Leu Ala Arg Gly Leu Leu Cys Leu Asp Cys Ala Asn 10 15 20	342
gac cac aga tcc ccg gtt gag agg aat gcc cag acc aca ctc atc cta Asp His Arg Ser Pro Val Glu Arg Asn Ala Gln Thr Thr Leu Ile Leu 25 30 35	390
Cac tca tcc cta tac tca ttg tcc ctt ggg aac caa ctg cag gga gga His Ser Ser Leu Tyr Ser Leu Ser Leu Gly Asn Gln Leu Gln Gly Gly 40 45 50 55	438
ggg gaa atg gcc acc act gga ggg agt act cag cag gcc aag act tat Gly Glu Met Ala Thr Thr Gly Gly Ser Thr Gln Gln Ala Lys Thr Tyr 60 65 70	486
ggg gga ctc ttc caa att ggg gcc atg gaa ccg gca cta ttt cta ctc Gly Gly Leu Phe Gln Ile Gly Ala Met Glu Pro Ala Leu Phe Leu Leu 75 80 85	534
ttt att ttc ctt ttg gca tcc ttt tgg gtt cac ccg agc tat aga ata Phe Ile Phe Leu Leu Ala Ser Phe Trp Val His Pro Ser Tyr Arg Ile 90 95 100	582

Thr Tyr * 105	030
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aaa ctc ttc cta ttc ttc acc tta ttg gtt aat tta ttt att acc aat Lys Leu Phe Leu Phe Phe Thr Leu Leu Val Asn Leu Phe Ile Thr Asn 10 15 20	159
gac caa ctc agt gtg ggt agt att ttt ctc agc ttc cag ctc cca gct Asp Gln Leu Ser Val Gly Ser Ile Phe Leu Ser Phe Gln Leu Pro Ala 25 30 35	207
ttc ttt ctt gat atg gct gaa ttt tga gatac tcaaagcaag cagaccataa Phe Phe Leu Asp Met Ala Glu Phe * 40 45	259
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gggttattat ccctttttaa agaactactt ataggatggt ggcaggacct ttgaaattgc	379
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taacatgact attatcatca tgctgctgct atcgtggata tttgcatttt atagctttgg	619
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tta cac gtt ctg gtg aca gct ctg tcc tct cat tcc act ggg cgt agg Leu His Val Leu Val Thr Ala Leu Ser Ser His Ser Thr Gly Arg Arg 5 10 15 20	164
ggt act aac tgc ttc atg tta ctt tcc tca ggg aat cat cct atc cct Gly Thr Asn Cys Phe Met Leu Leu Ser Ser Gly Asn His Pro Ile Pro 25 30 35	212
tgt ggt tcc ctg aca ccc tac cca cac ctt tga aaatggag cctttattac Cys Gly Ser Leu Thr Pro Tyr Pro His Leu * 40 45	263
atactcctcg ggtctccccc tactaaagtg ggccgtctct ttcctgttga agcattgact	323
gatacactgg cgaaagggaa caccctgcct gcccttcacc ccctcccaag agcctaaaga	383
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tgagatactt geteagatta tetatetgtt gtgaacteca ttttaaaaage aceteactat	180
accatgettg aagteaggta gtetgtagae tteateaeag eccetttata tataattaet	240
tototoacgg aggagtatgg tgtatttacc tgtatctttg aatggottaa gattagca tgc ttc agc tat gtt ctt gct cct atc aaa gtg aaa cct ggg ggt ggc Met Leu Ile Leu Ser His Ser Lys Ile Gln Val Asn Thr Pro Tyr Ser 1 5 10 15	298 346
tca gag aca cgt gac ggg ttt aga atc cca gag agc aca ccc tca cta Ser Val Arg Glu Val Ile Ile Tyr Lys Gly Ala Val Met Lys Ser Thr 20 25 30	394
aag gcc ggt tac tgc gac cat aaa cac ttett gcccacaatt catetttta Asp Tyr Leu Thr Ser Ser Met Val * 35 40	446
aaatttttcg tttcagaaaa tgtgatgttc tgaatcgtgg attttcaggt tacaatacca	506
ggtgggccaa aattateett ccaagattaa tcaggaaagg aaacagtttg gacateecag	566

tagcagttac aattttcttt ggggccaatg acagtgcact aaaagatgag aatcccaagc

PCT/US01/02623

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agt ttt cta ttg tac tcg aaa aga ttt gaa ggt ata tcc ttc tgt gtc Ser Phe Leu Leu Tyr Ser Lys Arg Phe Glu Gly Ile Ser Phe Cys Val 15 20 25	160
caa aag gtc agt ata ata tta tgt ata cat tat ctt cgt agc aca act Gln Lys Val Ser Ile Ile Leu Cys Ile His Tyr Leu Arg Ser Thr Thr 30 35 40	208
att tgg aat aag ctt ttc ttc aga gat gta tcg gca taa aggagctctg Ile Trp Asn Lys Leu Phe Phe Arg Asp Val Ser Ala * 45 50 55	257
atttgtttaa atattttaaa aggtattaaa atatattttc atttgagaac ctcccctata	317
tactcaggaa agctcacctt ttcaaaacct gagtgttaac tctttccaaa cgttctgtaa	377
tgtttatcaa aaacaaaaaa taatgaaaag aggtgaacat tattttggag agcctcattg	437
gcttcatcta ctcagatcat ccacaatcac tggagaggag gcagaatttt gtcactggga	497
cagcagtcac ttgacccaga atcetetacc gattecetec agggageeet teccattgge	557
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aaacatttct aatgtttata tcacttgctt gtaaatc atg cat ttt cct gtg aac 175

## Met His Phe Pro Val Asn 1 5

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gcc Ala	act Thr	ttt Phe 25	ttg Leu	aga Arg	aaa Lys	aaa Lys	tta Leu 30	agt Ser	aag Lys	gta Val	gcc Ala	ttc Phe 35	agt Ser	tgt Cys	ctt Leu	271
gtt Val	gaa Glu 40	ttt Phe	ttc Phe	tac Tyr	tat Tyr	tgt Cys 45	tat Tyr	tat Tyr	ttt Phe	tta Leu	gac Asp 50	ttt Phe	gct Ala	agt Ser	agt Ser	319
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ctg Leu	tca Ser	ccc Pro	agg Arg	ctg Leu 75	gag Glu	tgc Cys	agt Ser	gac Asp	acg Thr 80	atc Ile	ttg Leu	gct Ala	cac His	tgc Cys 85	aac Asn	415
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aca	cagt	caa	aaat	tcaa	ga c	gggc	atgg	t gg	ctca	tggc	tgc	aatc	cca	gcac	tttagg	943
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205

Leu Phe Cys Leu Asn Thr Gln His Leu Ser Val Arg Asn Asn Phe Val

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Gln Leu Lys Gln Glu Leu Arg Leu Asn Tyr Leu Thr Leu Thr Gln Phe
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Trp Gln Arg Cys Tyr Ser Glu Met Ile Phe Phe Cys Leu Ser Lys Val
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Phe Leu His Val Phe Gln Asp Gly Leu Glu His His Leu Glu \*
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Leu Ser Lys Val
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245 250 255 245 250 Met Phe Ala Thr Thr Leu Gly Val Met Gly Leu Trp Ser Gly Ile Ile 260 270 265 Ile Cys Thr Val Phe Gln Ala Val Cys Phe Leu Gly Phe Ile Ile Gln 275 280 285 Leu Asn Trp Lys Lys Ala Cys Gln Gln Gly Ala Leu Lys Thr Leu Lys 295 300 Glu Phe \* 305 306

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<210> 312 <211> 65 <212> PRT <213> Homo sapiens

<210> 313 <211> 47 <212> PRT <213> Homo sapiens

<210> 314 <211> 101 <212> PRT <213> Homo sapiens

(213) HOMO Sapiens

<400> 314 Met Ser Leu Val Leu Asn Gln Ile Glu Leu Ser Glu Lys Gly Met Ala 10 Val Lys Asn Val Ala Leu Val Ile Thr Trp Ala Tyr Gly Phe Val Lys 25 Val Thr Leu Ser Leu Leu Val Phe Cys Val Tyr Cys Met Tyr Val Ile 35 40 Leu His Leu Arg Met Tyr Ile Thr His Lys Gly Ala Cys Arg His Met 55 60 Ser Ala Ser Trp Leu Ala Thr Asn Cys Leu Trp Pro Trp Gly Cys His · 75 Ser Thr Phe His Leu Glu Ile Glu Asn Asn Asn Thr Ile Ile Leu Leu 90 Glu Leu Cys Ala 100

<210> 315

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<210> 310
<211> 278
<212> PRT
<213> Homo sapiens
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<400> 310 Met Ala Gly Pro Glu Leu Leu Leu Asp Ser Asn Ile Arg Leu Trp Val 5 10 Val Leu Pro Ile Val Ile Ile Thr Phe Phe Val Gly Met Ile Arg His 20 25 Tyr Val Ser Ile Leu Leu Gln Ser Asp Lys Leu Thr Gln Glu Gln 35 40 Val Ser Asp Ser Gln Val Leu Ile Arg Ser Arg Val Leu Arg Glu Asn 60 Gly Lys Tyr Ile Pro Lys Gln Ser Phe Leu Thr Arg Lys Tyr Tyr Phe 70 75 Asn Asn Pro Glu Asp Gly Phe Phe Lys Lys Thr Lys Arg Lys Val Val 85 90 Pro Pro Ser Pro Met Thr Asp Pro Thr Met Leu Thr Asp Met Met Lys 105 100 110 Gly Asn Val Thr Asn Val Leu Pro Met Ile Leu Ile Gly Gly Trp Ile 115 120 125 Asn Met Thr Phe Ser Gly Phe Val Thr Thr Lys Val Pro Phe Pro Leu 135 140 Thr Leu Arg Phe Lys Pro Met Leu Gln Gln Gly Ile Glu Leu Leu Thr 150 155 160 Leu Asp Ala Ser Trp Val Ser Ser Ala Ser Trp Tyr Phe Leu Asn Val 165 170 175 Phe Gly Leu Arg Ser Ile Tyr Ser Leu Ile Leu Gly Gln Asp Asn Ala 180 185 190 Ala Asp Gln Ser Arg Met Met Gln Glu Gln Met Thr Gly Ala Ala Met 195 200 205 Ala Met Pro Ala Asp Thr Asn Lys Ala Phe Lys Thr Glu Trp Glu Ala 210 215 220 Leu Glu Leu Thr Asp His Gln Trp Ala Leu Asp Asp Val Glu Glu 225 230 235 Leu Met Gly Gln Arg Pro Pro Leu Arg Arg His Val Gln Lys Gly Ile 245 250 255 Thr Asp Leu Tyr Phe Leu Lys Thr Glu Gln Gly Leu Ala Val Ser Gly 270 260 265 Thr Trp Ser Cys Thr \* 275 277

<210> 311 <211> 52 <212> PRT <213> Homo sapiens

PCT/US01/02623 WO 01/55437

<213> Homo sapiens

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<210> 308 <211> 70 <212> PRT <213> Homo sapiens

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<210> 309 <211> 150 <212> PRT

<213> Homo sapiens

<400> 309 Met Val Phe Leu Thr Ala Gln Leu Trp Leu Arg Asn Arg Val Thr Asp 10 Arg Tyr Phe Arg Ile Gln Glu Val Leu Lys His Ala Arg His Phe Arg 20 25 Gly Arg Lys Asn Arg Cys Tyr Arg Leu Ala Val Arg Thr Val Ile Arg 35 40 Ala Phe Val Lys Cys Thr Lys Ala Arg Tyr Leu Lys Lys Lys Asn Met 55 60 Arg Thr Leu Trp Ile Asn Arg Ile Thr Ala Ala Ser Gln Glu His Gly 70 75 Leu Lys Tyr Pro Ala Leu Ile Gly Asn Leu Val Lys Cys Gln Val Glu 85 90 Leu Asn Arg Lys Val Leu Ala Asp Leu Ala Ile Tyr Glu Pro Lys Thr 100 105 Phe Lys Ser Leu Ala Ala Leu Ala Ser Arg Arg Arg His Glu Gly Phe 120 125 Ala Ala Ala Leu Gly Asp Gly Lys Glu Pro Glu Gly Ile Phe Ser Arg 135 140 Val Val Gln Tyr His \* 145 149

<210> 304 <211> 49 <212> PRT <213> Homo sapiens

<210> 305 <211> 107 <212> PRT <213> Homo sapiens

<400> 305 Met Leu Ala Thr Leu Ala Cys Met Ala Ile Pro Trp Thr His Leu Gly 1 5 10 15 Cys Ser Cys Leu Leu Ala Cys Leu Pro Phe Ser His His Leu Gly Leu 20 25 30 Ser Glu Asp Ile Ile Ser Ser Glu Lys Pro Ser Val Thr Met Leu Ser 35 40 45 Lys Ile Leu Gln His Phe Ser His Pro Leu Ser His Tyr Ser Ala Phe 55 60 Ser Glu Thr Leu Val Leu Pro Glu Thr Tyr Leu Phe Thr Cys Leu Val 65 70 75 Ser Phe Leu Pro His Tyr His Val Ser Phe Leu Arg Val Arg Asp Leu 85 90 Val Arg Asp Asn His Cys Ile Leu Arg Val 100 105 106

<210> 306 <211> 47 <212> PRT <213> Homo sapiens

<210> 307
<211> 70
<212> PRT

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Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
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Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
             85
                        90
Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
         100
                  105
                                         110
Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
   115 120
                                       125
Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
           135
                                  140
Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
               150
                               155
Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
          165
                  170
Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
        180
                   185
Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
    195
                      200
Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
                   215
                            220
Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
              230 235 240
Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
            245
                             250
Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
       260
                          265
Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
    275
                      280
                                      285
Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
                   295
                                  300
Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
              310
                       315
Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
            325
                            330
Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
        340
                 345
Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
    355 360
                               365
Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
                   375
                                 380
Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
              390
                       395 400
Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
            405
                          410
His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg *
         420
                         425
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<210> 303 <211> 56 <212> PRT <213> Homo sapiens

<400> 303

 Phe Ile Ile Val Thr Phe Lys Trp Ile Asp Lys Phe Ile Leu Asn Ile
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 70
 75
 80

 Ser Ile Leu Ile Ser Asn Thr Val Asn Val Asn Ser His Asn Pro His
 85
 90
 95

 Lys Gln Lys Phe Phe Gly Asp Leu Ser Asn Phe
 105
 107

<210> 301
<211> 228
<212> PRT
<213> Homo sapiens

<400> 301

Met Leu Val Val Lys Gly Val Cys Phe Lys Ala His Lys Asn Val Leu 10 Ala Ala Phe Ser Gln Tyr Phe Arg Asn Val Gln Gln Met His Ser Arg 20 25 Thr Lys Arg Trp Met Asn Arg Ile Arg Met Leu His His Gln Leu Ile 40 Val Ile Thr Pro Gln Val Lys Ser Gln Asn Lys Leu Leu Ile Leu Gln 60 50 55 Met Ala Ala Ala Gln Asn Cys Leu Ser Asn Ser Gln Ile Thr Ile Thr 65 70 75 Asn Ser Glu Thr Phe Thr Pro Val Asn Asp Ser Ala Pro His Pro Glu 90 95 85 Ser Asp Ala Thr Cys Gln Gln Pro Val Lys Gln Met Arg Leu Lys Lys 100 105 110 Ala Ile His Leu Lys Lys Leu Asn Phe Leu Lys Ser Gln Lys Tyr Ala 125 115 120 Glu Gln Val Ser Glu Pro Lys Ser Asp Asp Gly Leu Thr Lys Arg Leu 135 140 Glu Ser Ala Ser Lys Asn Thr Leu Glu Lys Ala Ser Ser Gln Ser Ala 150 155 Glu Glu Lys Glu Ser Glu Glu Val Val Ser Cys Glu Asn Phe Asn Cys 165 170 Ile Ser Glu Thr Glu Arg Pro Glu Asp Pro Ala Ala Leu Glu Asp Gln 180 185 190 Ser Gln Thr Leu Gln Ser Gln Arg Gln Tyr Ala Cys Glu Leu Cys Gly 195 200 205 Lys Pro Phe Lys His Pro Ser Asn Leu Glu Leu His Lys Arg Ser His 215 Thr Gly Asn \* 225 ·227

<210> 302 <211> 430 <212> PRT <213> Homo sapiens

<400> 302

 Met
 Cys
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 Trp
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 Met Leu Gly Trp Gln Ile Trp Arg Leu Arg Pro Gln Leu Leu Ser Phe

 1
 5
 10
 15

 His Thr Gln Asp Arg Cys His Trp Ser Ile Thr Ser Gln Cys Ser Lys

 20
 25
 30

 Pro Glu Ser Gln Glu Ser Phe Leu Ser Thr Ile His Leu Leu Glu Gly
 45

 Ala Gln Glu Gly Thr Pro Thr Glu \*
 55
 56

<210> 298 <211> 72 <212> PRT <213> Homo sapiens

<210> 299 <211> 59 <212> PRT <213> Homo sapiens

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<210> 296 <211> 38 <212> PRT <213> Homo sapiens

<210> 297 <211> 57 <212> PRT <213> Homo sapiens

<400> 297

Glu Arg Lys Ala Thr Lys Arg Val Lys Arg Lys Gln Asp Val Thr Gly 105 Asn Asp Pro His Ser Pro Ser Leu Ser Ser Gly Gly Pro Ile His Lys 115 120 125 Ala Asn Thr Ser Gly Arg Leu Lys Val Ser Asp Arg Gly Thr Ala Glu 135 140 Arg Arg Gly Gly Phe Leu Ala Arg Trp Arg Val Phe Thr Val Cys Trp 150 155 Val Gln Ala Cys Val Cys Pro Gly Lys Met Leu Ala Met Gly Ala Leu 170 175 Ala Gly Phe Trp Ile Leu Cys Leu Leu Thr Tyr Gly Tyr Leu Ser Trp 185 Gly Gln Ala Leu Glu Glu Glu Glu Gly Ala Leu Leu Ala Gln Ala 195 205 200 Gly Glu Lys Leu Glu Pro Ser Thr Thr Ser Thr Ser Gln Pro His Leu 215 Ile Phe Ile Leu Ala Asp Asp Gln Gly Phe Arg Asp Val Gly Tyr His 230 235 Gly Ser Glu Ile Lys Thr Pro Thr Leu Asp Lys Leu Ala Ala Glu Gly 245 250 Val Lys Leu Glu Asn Tyr Tyr Val Gln Pro Ile Cys Thr Pro Ser Arg 270 265 Ser Gln Phe Ile Thr Gly Lys Tyr Gln Ile His Thr Gly Leu Gln His 275 280 285 Ser Ile Ile Arg Pro Thr Gln Pro Asn Cys Leu Pro Leu Asp Asn Ala 295 Thr Leu Pro Gln Lys Leu Lys Glu Val Gly Tyr Ser Thr His Met Val 310 315 Gly Lys Trp His Leu Gly Phe Tyr Arg Lys Glu Cys Met Pro Thr Arg 330 Arg Gly Phe Asp Thr Phe Phe Gly Ser Leu Leu Gly Ser Gly Asp Tyr 340 345 350 Tyr Thr His Tyr Lys Trp Asp Ser Pro Trp Asp Val Trp Leu 360

<210> 293 <211> 113 <212> PRT <213> Homo sapiens

<400> 293

Met Ala Tyr Ile Ile Gln Pro Ser Ser Thr Ser Val Ile Ser Val Lys 10 Leu Ser Leu Gly His Cys Ala Ser Ala Thr Leu Thr Ser Leu His Ile 20 25 Ser His Ile His Gln Ala Cys Ser Cys Leu Gly Ala Phe Val Leu Thr 35 40 45 Met Phe Cys Ser Glu Asn Thr Leu Pro Gln Asp Ile Leu Gln Leu Ser 55 60 Tyr Cys Ile Gln Leu Ser Ala Gln Val Leu Thr Asp Glu Thr Cys His 70 75 Pro Tyr Ser Thr Pro Cys Ser Ala Leu Leu Asn Ser Asn Cys Thr Tyr 85 90 Gly Pro Leu Asn Asn Ile His Leu Val Thr Tyr Phe Tyr Leu Ser Ala 113

<210> 294

<211> 107 <212> PRT <213> Homo sapiens

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<210> 291 <211> 96 <212> PRT <213> Homo sapiens

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<210> 292 <211> 366 <212> PRT <213> Homo sapiens

<400> 292 Met Leu Tyr Trp Val Val Ile His Phe Gly Ala Arg Gly Pro Gly Gly 5 10 Arg Arg Lys Arg Arg Thr Thr Asn Gly Glu Gly Arg Asn Ala Ala Arg 20 25 His Ala Gly Lys Glu Gly Asn Pro Arg Lys Pro Thr Gly Asn Ala Gln 45 40 35 Thr Pro Met Asp Pro Arg Lys Arg Lys Lys Gly Ser Leu Thr Pro Gly 60 55 Pro Asn Arg Arg Gln Glu Ser Glu Gly Ala Arg Arg Gln Ser Arg 75 70 Arg Gly Glu Asn Gly Ser Glu Ala Ala Gln Ser Pro Ser Arg Gly Thr 90

<400> 287 Met Phe Leu Arg Gly Ile Pro Ser Arg Arg Glu Ser Leu Lys Thr Asn 10 Thr His Arg Ser Trp Arg Trp Ala Pro His Ser Pro Leu Asp Leu Thr 20 25 Ile Arg Asn Leu Leu Cys His Leu Phe Ile Lys Leu Ser Gln Ala Gln 35 40 Lys Ala Cys Pro Asn His Met Leu Arg Ala Lys Gln Met Glu Gln Lys 55 60 Leu Pro Gln Ala Ala Gly Ser His Tyr Gly Trp Asp Glu Ala Arg Thr 70 75 Trp Ala His Thr Gly Cys Lys Ala Ala Asp Ala Trp Val Asp Pro Gly 85 90 Val Pro Glu Gln Asp Leu Pro Ala Phe Asn 100

<210> 288 <211> 114 <212> PRT <213> Homo sapiens

<400> 288 Met Ser Ser Trp Phe Leu Arg Ala Gly His Gly Leu Ile Trp Val Leu 10 Phe Phe Arg Ile Gly Gln Ala Ala Val Gly Val Ser Ala Gly Pro Gly 20 25 Gly Ser Pro Lys Ala His Leu Gly Arg Val Ala Ser Gln His Pro His 35 40 45 Gly Ala Glu Ser Arg Ala Cys Leu Leu Ala Arg Gly Leu Pro Lys Ala 55 60 Leu Ser Ser Met Leu Ala Val Asp Cys Arg Pro Arg Ser Gly Pro Leu 70 75 His Arg Ala Ala His Ile Met Ala Ala Ser Leu Ile Ser Lys Pro Val 85 90 Arg Gly Cys Leu Ser Glu Asp Asp Ile Pro Ser Pro Leu Ser Asp Ser 105 Ala Tyr 114

<210> 289 <211> 52 <212> PRT <213> Homo sapiens

<210> 290

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn 435 440 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr 455 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys 465 470 474

<210> 285 <211> 48 <212> PRT <213> Homo sapiens

<400> 285 Met Leu Gly Ile Cys Leu Cys Ser Ile Cys Val Leu Arg Leu Cys Leu 10 15 1 5 Glu Lys Ser Lys Ile Phe Pro Pro Pro Arg Thr Ser Asp His Ser Leu 20 25 Glu Gly Ser Val Thr Pro Val Glu Asn Ala Ala Arg Ser Gly Met \* 35 40 45 47

<210> 286 <211> 183 <212> PRT

<213> Homo sapiens

<400> 286 Met Asn Ser Asn Leu Pro Ala Glu Asn Leu Ser Ile Ala Val Asn Met 5 10 Thr Lys Thr Leu Pro Thr Ala Val Thr His Gly Phe Asn Ser Thr Asn 20 25 Asp Pro Pro Ser Met Ser Ile Thr Arg Leu Phe Ser Ala Leu Leu Glu 35 40 Cys Phe Gly Ile Val Leu Cys Gly Tyr Ile Ala Gly Arg Ala Asn Val 55 60 Ile Thr Ser Thr Gln Ala Lys Gly Leu Gly Asn Phe Val Ser Arg Phe 65 70 75 Ala Leu Pro Ala Leu Leu Phe Lys Asn Met Val Val Leu Asn Phe Ser 85 90 95 Asn Val Asp Trp Ala Phe Leu Tyr Ser Ile Leu Ile Ala Lys Ala Ser 100 105 Val Phe Phe Ile Val Cys Val Leu Thr Leu Leu Val Ala Ser Pro Asp 120 Ser Arg Phe Ser Lys Ala Gly Leu Phe Pro Ile Phe Ala Thr Gln Ser 135 140 Asn Asp Phe Ala Leu Gly Tyr Pro Ile Gly Lys Leu Ile Phe Ile Phe 145 150 155 160 Gln Val Phe Lys Lys Phe Asn Phe Asn Leu Phe Arg His Leu Leu Val 165 170 Thr Asp Ser Tyr Ser His Ile 180 183

<210> 287 <211> 106 <212> PRT <213> Homo sapiens

<210> 284 <211> 474 <212> PRT <213> Homo sapiens

<400> 284 Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly 10 Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys 20 25 Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe 35 40 Ser Asp Tyr Trp Val Ala Trp Val Arg Gln Ser Pro Asp Lys Gly Leu 55 Ala Trp Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser 75 Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser 85 90 Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Asp Ser Asp Thr Ala Met 100 105 110 Tyr Tyr Cys Ala Arg Gly Ala Arg Gly Thr Ala Pro Ser Tyr His Tyr 115 120 Tyr Gly Leu Asp Val Trp Gly Arg Gly Thr Ser Val Thr Val Ser Ser 130 135 140 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys 150 155 160 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr 170 165 175 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser 185 180 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser 195 200 205 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr 215 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 230 235 Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys 245 250 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro 260 265 270 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys 275 280 285 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp 290 295 300 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 310 315 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu 325 330 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn 340 345 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 355 360 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu 375 380 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr 390 395 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn 405 410 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe 420 425

<210> 282 <211> 113 <212> PRT <213> Homo sapiens

<400> 282 Met Cys His Trp Gln Asn Ser Phe Leu Cys Gln Ser Phe Leu Thr Phe 10 Gly Ser Ile Leu Ala Leu Leu Ala Gly Lys Ala Cys Tyr Pro Glu Ser 20 25 Glu Ser Ile Arg Glu Leu Phe Met Trp Ser Leu Glu Leu Tyr Ser Leu 40 35 Pro Phe Tyr Leu Phe Phe Lys Leu Ser Pro Leu Asn Leu Pro Gly Lys 50 60 Leu Gly Leu Ile Glu Thr Leu Ser Thr Cys Leu Gly Gln Lys Leu Asp 70 75 Pro Val Leu Glu Thr Leu Gln Arg Val Arg Ser Met Ala Ser Leu Ile 90 Ala Asn Phe Phe Val Pro Phe Ile Gln Lys Lys Gly Gln Leu Ile Thr 105

<210> 283 <211> 231 <212> PRT

<213> Homo sapiens

<400> 283 Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly 10 Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser 20 25 Pro Gly Lys Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp 35 40 Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Ala Gly Gln Ser Pro Val Leu 50 55 60 Val Ile Tyr Arg His Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe 65 70 75 80 Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr 85 90 95 Gln Val Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser 105 Ile Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro 120 125 115 Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu 135 140 Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro 150 155 160 Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala 165 170 175 Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala 180 185 . 190 Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg 200 205 Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr 215 Val Ala Pro Thr Glu Cys Ser 230 231

Gly Ser Ser Ser Leu Ser Leu Thr Arg Lys Asn Ser Pro Lys Ser Gly Ser Pro Lys Ser Ser Ser Leu Leu Lys Leu Lys Ala Glu Lys Asn Ala Gln Ala Glu Met Gly Lys Asn His Ser Ser Ala Ser Phe Ser Ser Ser Ile Thr Ile Asn Thr Thr Cys Cys Ser Ser Ser Ser Ser Ser Ser Ser Leu Ser Lys Thr Ser Gly Asp Leu Lys Pro Arg Ser Ala Ser Asp Ala Gly Ile Arg Gly Thr Pro Lys Val Arg Ala Lys Lys Asp Ala Asp 565 570 Ala Asn Ala Gly Leu Thr Ser Cys Pro Arg Ala Lys Pro Ser Val Arg Pro Lys Pro Phe Leu Asn Arg Ala Glu Ser Gln Ser Gln Glu Lys Met Asp Ile Ser Thr Leu Arg Arg Gln Leu Arg Pro Thr Gly Gln Leu Arg Gly Gly Leu Lys Gly Ser Lys Ser Glu Asp Ser Glu Leu Pro Pro Gln Thr Ala Ser Glu Ala Pro Ser Glu Gly Ser Arg Arg Ser Ser Ser Asp Leu Ile Thr Leu Pro Ala Thr Thr Pro Pro Cys Pro Thr Lys Lys Glu Trp Glu Gly Pro Ala Thr Ser Tyr Met Thr Cys Ser Ala Tyr Gln Lys Val Gln Asp Ser Glu Ile Ser Phe Pro Ala Gly Val Glu Val Gln Val Leu Glu Lys Gln Glu Ser Gly Trp Trp Tyr Val Arg Phe Gly Glu Leu Glu Gly Trp Ala Pro Ser His Tyr Leu Val Leu Asp Glu Asn Glu Gln 725 730 Pro Asp Pro Ser Gly Lys Glu Leu Asp Thr Val Pro Ala Lys Gly Arg Gln Asn Glu Gly Lys Ser Asp Ser Leu Glu Lys Ile Glu Arg Arg Val Gln Ala Leu Asn Thr Val Asn Gln Ser Lys Lys Ala Thr Pro Pro Ile Pro Ser Lys Pro Pro Gly Gly Phe Gly Lys Thr Ser Gly Thr Pro Ala Val Lys Met Arg Asn Gly Val Arg Gln Val Ala Val Arg Pro Gln Ser Val Phe Val Ser Pro Pro Pro Lys Asp Asn Asn Leu Ser Cys Ala Leu Arg Arg Asn Glu Ser Leu Thr Ala Thr Asp Gly Leu Arg Gly Val Arg Arg Asn Ser Ser Phe Ser Thr Ala Arg Ser Ala Ala Ala Glu Ala Lys Gly Arg Leu Ala Glu Arg Ala Ala Ser Gln Gly Ser Asp Ser Pro Leu Leu Pro Ala Gln Arg Asn Ser Ile Pro Val Ser Pro Val Arg Pro Lys Pro Ile Glu Lys Ser Gln Phe Ile His Asn Asn Leu Lys Asp Val Tyr Val Ser Ile Ala Asp Tyr Glu Gly Asp Glu Glu Thr Ala Gly Phe Gln Glu Gly Val Ser Met Glu Val Leu Glu Arg Asn Pro Asn Gly Trp Trp Tyr Cys Gln Ile Leu Asp Gly Val Lys Pro Phe Lys Gly Trp Val Pro Ser Asn Tyr Leu Glu Lys Lys Asn \* 

<213> Homo sapiens

<400> 281 Met Ile Leu Glu Gln Tyr Val Val Val Ser Asn Tyr Lys Lys Gln Glu 10 Asn Ser Glu Leu Ser Leu Gln Ala Gly Glu Val Val Asp Val Ile Glu 20 25 Lys Asn Glu Ser Gly Trp Trp Phe Val Ser Thr Ser Glu Glu Gln Gly 40 Trp Val Pro Ala Thr Tyr Leu Glu Ala Gln Asn Gly Thr Arg Asp Asp 50 55 Ser Asp Ile Asn Thr Ser Lys Thr Gly Glu Val Ser Lys Arg Arg Lys 75 70 Ala His Leu Arg Arg Leu Asp Arg Arg Trp Thr Leu Gly Gly Met Val 90 85 Asn Arg Gln His Ser Arg Glu Glu Lys Tyr Val Thr Val Gln Pro Tyr 110 100 105 Thr Ser Gln Ser Lys Asp Glu Ile Gly Phe Glu Lys Gly Val Thr Val 115 120 125 Glu Val Ile Arg Lys Asn Leu Glu Gly Trp Trp Tyr Ile Arg Tyr Leu 135 140 Gly Lys Glu Gly Trp Ala Pro Ala Ser Tyr Leu Lys Lys Ala Lys Asp 150 155 Asp Leu Pro Thr Arg Lys Lys Asn Leu Ala Gly Pro Val Glu Ile Ile 165 170 Gly Asn Ile Met Glu Ile Ser Asn Leu Leu Asn Lys Lys Ala Ser Gly 185 180 Asp Lys Glu Thr Pro Pro Ala Glu Gly Glu Gly His Glu Ala Pro Ile 195 200 Ala Lys Lys Glu Ile Ser Leu Pro Ile Leu Cys Asn Ala Ser Asn Gly 220 215 Ser Ala Val Gly Val Pro Asp Arg Thr Val Ser Arg Leu Ala Gln Gly 230 235 Ser Pro Ala Val Ala Arg Ile Ala Pro Gln Arg Ala Gln Ile Ser Ser 245 250 255 Pro Asn Leu Arg Thr Arg Pro Pro Pro Arg Arg Glu Ser Ser Leu Gly 265 270 Phe Gln Leu Pro Lys Pro Pro Glu Pro Pro Ser Val Glu Val Glu Tyr 280 Tyr Thr Ile Ala Glu Phe Gln Ser Cys Ile Ser Asp Gly Ile Ser Phe 295 300 Arg Gly Gly Gln Lys Ala Glu Val Ile Asp Lys Asn Ser Gly Gly Trp 310 315 320 Trp Tyr Val Gln Ile Gly Glu Lys Glu Gly Trp Ala Pro Ala Ser Tyr 325 330 335 Ile Asp Lys Arg Lys Lys Pro Asn Leu Ser Arg Arg Thr Ser Thr Leu 340 345 350 Thr Arg Pro Lys Val Pro Pro Pro Ala Pro Pro Ser Lys Pro Lys Glu 355 360 365 Ala Glu Glu Gly Pro Thr Gly Ala Ser Glu Ser Gln Asp Ser Pro Arg 375 380 Lys Leu Lys Tyr Glu Glu Pro Glu Tyr Asp Ile Pro Ala Phe Gly Phe 390 395 Asp Ser Glu Pro Glu Leu Ser Glu Glu Pro Val Glu Asp Arg Ala Ser 405 410 415 Gly Glu Arg Arg Pro Ala Gln Pro His Arg Pro Ser Pro Ala Ser Ser 420 425 Leu Gln Arg Ala Arg Phe Lys Val Gly Glu Ser Ser Glu Asp Val Ala 435 440 445 Leu Glu Glu Glu Thr Ile Tyr Glu Asn Glu Gly Phe Arg Pro Tyr Ala 455 460 Glu Asp Thr Leu Ser Ala Arg Gly Ser Ser Gly Asp Ser Asp Ser Pro 470 475

<210> 280 <211> 301 <212> PRT <213> Homo sapiens

<400> 280 Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu 1 5 10 Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln 20 25 Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu 35 40 45 Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly 55 60 Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser 70 75 Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr 85 90 95 Ile Gly Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile 100 105 Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val 115 120 125 Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Leu Gln Arg Asp Phe 130 135 140 Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala 145 150 155 160 Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile 165 170 175 Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu 180 185 Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly 195 200 Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe 210 215 220 Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile 230 235 240 Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu 245 250 255 Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr 260 265 Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln 280 275 285 Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro 295 300 301

<210> 281 <211> 969 <212> PRT

<213> Homo sapiens

<400> 278 Met Glu Ser Ser Cys Leu Asp Ile Gly Ser Val Pro Met Gly Thr Ser 10 Cys Leu Asp Ser Trp Pro Val His Ile Ile Ser Cys Leu Asp Ser Gly 20 25 Ser Val Arg Ile Lys Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met 35 40 Gly Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met Gly Thr Ser Cys 55 Leu Gly Ser Glu Pro Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu 70 75 Ser Val His Met Gly Thr Ser Cys Leu Gly Ser Glu Ser Val His Met 85 90 Gly Thr Ser Cys Leu Ala Ser Gly Pro Val His Met Gly Thr Ser Cys 100 105 110 Leu Gly Ser Gly Pro Val His Met Gly Thr Ser Cys Leu Gly Ser Gly 115 120 125 Ser Glu His Met Gly Thr Ser Arg Leu Asp Ser Gly Pro Val His Val 130 135 140 Gly Thr Ser Cys Leu Gly Ser Gly Ser Glu His Val Gly Thr Ser Cys 150 155 Leu Gly Ser Glu Tyr Val Tyr Thr Gly Thr Ser Arg Leu Asp Ser Gly 165 170 175 Pro Val His Met Gly Thr Ser Cys Leu Asp Ser Ala Ser Glu His Met 190 180 185 Gly Thr Ser Ser Leu Asp Ser Ala Ser Glu Leu Val Asp Ile Thr Cys 195 200 205 Leu Ser Lys Val Ile Thr Pro Leu Gly Phe Trp Lys Asn His Gly Asp 210 215 220 Phe Cys Pro Gly Lys Arg Tyr Asp Ala Ile Pro Leu 230 235 236

<210> 279 <211> 224 <212> PRT <213> Homo sapiens

<400> 279 Met Glu Ser Ser Cys Leu Asp Ile Gly Ser Val His Met Gly Thr Ser 1 5 10 15 Cys Leu Asp Ser Trp Pro Val His Ile Ile Ser Cys Leu Asp Ser Gly 20 25 Ser Val Arg Ile Lys Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met 40 Gly Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu Pro Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu 70 75 Ser Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu Ser Val Tyr Met 85 90 95 Gly Thr Ser Cys Leu Ala Ser Gly Pro Val His Met Gly Thr Ser Cys 105 100 Leu Gly Ser Gly Ser Glu His Met Gly Thr Ser Arg Leu Asp Ser Gly 115 120 125 Pro Val His Val Gly Thr Ser Cys Leu Gly Ser Gly Ser Glu His Met 130 135 140 Gly Thr Ser Cys Leu Gly Ser Glu Ser Val Tyr Thr Gly Thr Ser Arg

Gly Tyr Gly Thr Pro Met Thr Ser Asn Ala Val Arg Met Glu Ala Val 180 185 190 Glu Arg Asn Val Gly Val Ile Val Ala Ala Val Leu Val Thr Leu Ile 195 200 205 Leu Leu Gly Ile Leu Val Phe Gly Ile Trp Phe Ala Tyr Ser Arg Gly 215 220 His Phe Asp Arg Thr Lys Lys Gly Thr Ser Ser Lys Lys Val Ile Tyr . 230 235 Ser Gln Pro Ser Ala Arg Ser Glu Gly Glu Phe Lys Gln Thr Ser Ser 250 Phe Leu Val 259

<210> 277 <211> 273 <212> PRT <213> Homo sapiens

<400> 277 Met Met Ile His Gly Phe Gln Ser Ser His Arg Asp Phe Cys Phe Gly 10 Pro Trp Lys Leu Thr Ala Ser Lys Thr His Ile Met Lys Ser Ala Asp Val Glu Lys Leu Ala Asp Glu Leu His Met Pro Ser Leu Pro Glu Met 35 40 45 Met Phe Gly Asp Asn Val Leu Arg Ile Gln His Gly Ser Gly Phe Gly 55 60 Ile Glu Phe Asn Ala Thr Asp Ala Leu Arg Cys Val Asn Asn Tyr Gln 70 75 Gly Met Leu Lys Val Ala Cys Ala Glu Glu Trp Gln Glu Ser Arg Thr 85 90 Glu Gly Glu His Ser Lys Glu Val Ile Lys Pro Tyr Asp Trp Thr Tyr 105 100 Thr Thr Asp Tyr Lys Gly Thr Leu Leu Gly Glu Ser Leu Lys Leu Lys 120 Val Val Pro Thr Thr Asp His Ile Asp Thr Glu Lys Leu Lys Ala Arg 135 140 Glu Gln Ile Lys Phe Phe Glu Glu Val Leu Leu Phe Glu Asp Glu Leu 150 155 His Asp His Gly Val Ser Ser Leu Ser Val Lys Ile Arg Val Met Pro 165 170 175 Ser Ser Phe Phe Leu Leu Leu Arg Phe Phe Leu Arg Ile Asp Gly Val 180 185 Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp Lys Thr 200 205 Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser Ser Leu 215 220 Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile Ser Gln 230 235 Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe Pro Glu 245 250 Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln Val Glu 265 270 272

<210> 278 <211> 236 <212> PRT

Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe 55 Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe 85 90 Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser 100 105 110 Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val 125 115 120 Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr 140 130 135 Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro 150 155 Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn 170 165 Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro 190 185 180 Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly 200 205 Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser 215 220 Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val 230 235 Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly 245 250 Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly 260 265 270 Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu 275 280 Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val 295

<210> 276 <211> 259 <212> PRT <213> Homo sapiens

<400> 276 Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile 10 Leu Ala Ile Leu Pro Glu Asn Asn Pro Val Lys Leu Ser Cys Ala Tyr 25 Ser Gly Phe Ser Ser Pro Arg Ala Ala Ser Tyr Glu Asp Arg Val Thr 40 Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val Thr Arg Glu Asp Thr 60 Gly Thr Tyr Thr Cys Met Val Phe Glu Glu Gly Gly Asn Ser Tyr Gly 65 70 75 Glu Val Lys Val Lys Leu Ile Val Leu Val Pro Pro Ser Lys Pro Thr 90 85 Val Asn Ile Pro Ser Ser Ala Thr Ile Gly Asn Arg Ala Val Leu Thr 100 105 110 Cys Ser Glu Gln Asp Gly Ser Pro Pro Ser Glu Tyr Thr Trp Phe Lys 115 120 125 Asp Gly Ile Val Met Pro Thr Asn Pro Lys Ser Thr Arg Ala Phe Ser 140 135 Asn Ser Ser Tyr Val Leu Asn Pro Thr Thr Gly Glu Leu Val Phe Asp 150 155 Pro Leu Ser Ala Ser Asp Thr Gly Glu Tyr Ser Cys Glu Ala Arg Asn 170 165

Asp Asp Pro Thr Leu Ala Ile Ala Leu Ala Ala Asn Ala Trp Ala Phe 330 325 Val Leu Phe Tyr Val Ile Pro Glu Val Ser Gln Val Thr Lys Ser Ser 340 345 350 Pro Glu Gln Ser Tyr Gln Gly Asp Met Tyr Pro Thr Arg Gly Val Gly 360 Tyr Glu Thr Ile Leu Lys Glu Gln Lys Gly Gln Ser Met Phe Val Glu 370 375 380 Asn Lys Ala Phe Ser Met Asp Glu Pro Val Ala Ala Lys Arg Pro Val 390 395 Ser Pro Tyr Ser Gly Tyr Asn Gly Gln Leu Leu Thr Ser Val Tyr Gln 410 405 415 Pro Thr Glu Met Ala Leu Met His Lys Val Pro Ser Glu Gly Ala Tyr 420 425 430 Asp Ile Ile Leu Pro Arg Ala Thr Ala Asn Ser Gln Val Met Gly Ser 440 Ala Asn Ser Thr Leu Arg Ala Glu Asp Met Tyr Ser Ala Gln Ser His 455 460 Gln Ala Ala Thr Pro Pro Lys Asp Gly Lys Asn Ser Gln Val Phe Arg 465 470 475 Asn Pro Tyr Val Trp Asp 485 486

<210> 274 <211> 118 <212> PRT <213> Homo sapiens

<400> 274

Met Val Lys Thr Asp Ala His Leu Lys Asn Pro Pro Phe Ala Pro Phe Arg Val Tyr Thr Leu Thr Leu Ser Leu Leu Leu Lys Leu Ser His Tyr 25 Ser Cys Leu Trp Val Lys Lys Asp Phe Lys Asp Ser Ser Phe Tyr Asn 35 45 40 Ser Asn Asn Asn Ser Asn Ser Asn His Cys Lys Ser Leu Leu Ser Thr 55 60 His Tyr Met Pro Gly Ala Val Ile Ser Asn Leu Cys Leu Ile Ser Cys 70 75 Lys Val Ser Ser Pro Ile Lys Gln Thr His Gly Ile Ser Met Leu 85 90 Gln Met Lys Arg Leu Lys His Thr Leu Ala Arg Leu Ala Pro Gly Thr 100 105 His Gly Gly Ser Gln Asn 115 118

<210> 275 <211> 299 <212> PRT <213> Homo sapiens

<400> 275

Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile 1  $\phantom{0}$  5  $\phantom{0}$  10  $\phantom{0}$  10  $\phantom{0}$  15  $\phantom{0}$  Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His 20  $\phantom{0}$  25  $\phantom{0}$  30  $\phantom{0}$  Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu 35  $\phantom{0}$  45

<400> 272 Met Lys Thr Leu Phe Leu Asn Thr Glu Tyr Leu Met Pro Phe Leu Leu 5 10 15 Asn Gln Cys Gly Ser Leu Leu Tyr Tyr Leu Thr Leu Ala Ser Thr Asp 20 25 Leu Thr Leu Ala Val Pro Ile Cys Asn Ser Leu Ala Ile Ile Phe Thr 40 Leu Ile Val Gly Lys Ala Leu Gly Glu Asp Ile Gly Gly Lys Arg Ala 55 Val Ala Gly Met Val Leu Thr Val Ile Gly Ile Ser Leu Cys Ile Thr 65 70 75 Ser Ser Val Ser Lys Thr Gln Gly Gln Gln Ser Thr Leu 85 90

<210> 273 <211> 486 <212> PRT <213> Homo sapiens

<400> 273

Met Arg Gly Arg Gly Ser Gln Gln Gln Gln Pro Thr Arg Arg Gln Gly
1 5 10 15 Gln Lys Leu Pro Ser Pro Ser Pro Ala Gly Lys Tyr Glu Ser Ala Gln 25 Pro Gly Gly Thr Gln Pro Glu Pro Gly Leu Gly Ala Arg Met Ala Ile 40 His Lys Ala Leu Val Met Cys Leu Gly Leu Pro Leu Phe Leu Phe Pro 55 60 Gly Ala Trp Ala Gln Gly His Val Pro Pro Gly Cys Ser Gln Gly Leu 75 70 Asn Pro Leu Tyr Tyr Asn Leu Cys Asp Arg Ser Gly Ala Trp Gly Ile 85 90 95 Val Leu Glu Ala Val Ala Gly Ala Gly Ile Val Thr Thr Phe Val Leu 100 105 110 Thr Ile Ile Leu Val Ala Ser Leu Pro Phe Val Gln Asp Thr Lys Lys 115 120 125 Arg Ser Leu Leu Gly Thr Gln Val Phe Phe Leu Leu Gly Thr Leu Gly 135 140 Leu Phe Cys Leu Val Phe Ala Cys Val Val Lys Pro Asp Phe Ser Thr 150 155 160 Cys Ala Ser Arg Arg Phe Leu Phe Gly Val Leu Phe Ala Ile Cys Phe 165 170 175 Ser Cys Leu Ala Ala His Val Phe Ala Leu Asn Phe Leu Ala Arg Lys 180 185 190 Asn His Gly Pro Arg Gly Trp Val Ile Phe Thr Val Ala Leu Leu 195 200 205 Thr Leu Val Glu Val Ile Ile Asn Thr Glu Trp Leu Ile Ile Thr Leu 215 220 Val Arg Gly Ser Gly Glu Gly Gly Pro Gln Gly Asn Ser Ser Ala Gly 230 235 240 Trp Ala Val Ala Ser Pro Cys Ala Ile Ala Asn Met Asp Phe Val Met 245 250 255 Ala Leu Ile Tyr Val Met Leu Leu Leu Leu Gly Ala Phe Leu Gly Ala 260 265 270 Trp Pro Ala Leu Cys Gly Arg Tyr Lys Arg Trp Arg Lys His Gly Val 285 275 280 Phe Val Leu Leu Thr Thr Ala Thr Ser Val Ala Ile Trp Val Val Trp 295 300 Ile Val Met Tyr Thr Tyr Gly Asn Lys Gln His Asn Ser Pro Thr Trp

Ile Gln Glu Ala Arg Ala Asp Leu Ala Arg Arg Gly Leu Arg Phe \* 115 120 125 127

<210> 270 <211> 132 <212> PRT <213> Homo sapiens

<400> 270 Met Lys Phe Arg Ile Val Thr Cys Gln Ser Asp Trp Arg Glu Leu Trp 10 1 Val Asp Asp Ala Ile Trp Arg Leu Leu Phe Ser Met Ile Leu Phe Val 25 20 Ile Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln Arg Phe Ala Phe 40 Ser Pro Leu Ser Glu Glu Glu Glu Glu Asp Glu Gln Lys Glu Pro Met 50 55 60 Leu Lys Glu Ser Phe Glu Gly Met Lys Met Arg Ser Thr Lys Gln Glu 65 70 75 Pro Asn Gly Asn Ser Lys Val Asn Lys Ala Gln Glu Asp Asp Leu Lys 85 90 Trp Val Glu Glu Asn Val Pro Ser Ser Val Thr Asp Val Ala Leu Pro 100 105 110 Ala Leu Leu Asp Ser Asp Glu Glu Arg Met Ile Thr His Phe Glu Arg 120 115 Ser Lys Met Glu 130 132

<210> 271 <211> 118 <212> PRT <213> Homo sapiens

<400> 271 Met Lys Thr Leu Phe Leu Asn Thr Glu Tyr Leu Met Pro Phe Leu Leu 1 5 10 Asn Gln Gly Gly Ser Leu Leu Tyr Tyr Leu Thr Leu Ala Ser Thr Asp 20 Leu Thr Leu Ala Val Pro Ile Cys Asn Ser Leu Ala Ile Ile Phe Thr 40 45 35 Leu Tle Val Gly Lys Ala Leu Gly Glu Asp Ile Gly Gly Lys Arg Ala · 50 55 60 Val Ala Gly Met Val Leu Thr Val Ile Gly Ile Ser Leu Cys Ile Thr 70 75 Ser Ser Val Pro Trp Thr Ala Glu Leu Gln Leu His Gly Lys Gly Gln 90 Leu Gln Thr Leu Ser Gln Lys Cys Lys Arg Glu Ala Ser Gly Thr Gln 100 105 Ser Glu Arg Phe Gly \* 115 117

<210> 272 <211> 94 <212> PRT <213> Homo sapiens

Gly Ile Arg Leu His Cys Ala Arg Gly Asn Val Leu Gly Asn Thr His 85 90 Val Val Glu Ser Gln Ser Gly Ser Trp Gly Glu Trp Ser Glu Pro Leu 105 Trp Cys Arg Gly Gly Ala Tyr Leu Val Ala Phe Ser Leu Arg Val Glu 125 120 115 Ala Pro Thr Thr Leu Gly Asp Asn Thr Ala Ala Asn Asn Val Arg Phe 130 135 140 Arg Cys Ser Asp Gly Glu Glu Leu Gln Gly Pro Gly Leu Ser Trp Gly 150 155 Asp Phe Gly Asp Trp Ser Asp His Cys Pro Lys Gly Ala Cys Gly Leu 170 175 Gln Thr Lys Ile Gln Gly Pro Arg Gly Leu Gly Asp Asp Thr Ala Leu 185 190 180 Asn Asp Ala Arg Leu Phe Cys Cys Arg Ser 202 200 195

<210> 268 <211> 112 <212> PRT <213> Homo sapiens

<400> 268 Met Arg Gln Val Ala Arg Val Ile Val Phe Leu Thr Leu Ser Thr Leu 10 15 Ser Leu Ala Lys Thr Thr Gln Pro Ile Ser Met Asp Ser Tyr Glu Gly 25 30 20 Gln Glu Val Asn Ile Thr Cys Ser His Asn Asn Ile Ala Thr Asn Asp 45 40 35 Tyr Ile Thr Trp Tyr Gln Gln Phe Pro Ser Gln Gly Pro Arg Phe Ile 55 Ile Gln Gly Tyr Lys Thr Lys Val Thr Asn Glu Val Ala Ser Leu Phe 65 70 75 80 Ile Pro Ala Asp Arg Lys Ser Ser Thr Leu Ser Leu Pro Arg Val Ser 85 90 Leu Ser Asp Thr Ala Val Tyr Tyr Cys Leu Val Gly Asp Thr Gln \* 105

<210> 269 <211> 128 <212> PRT <213> Homo sapiens

<400> 269 Met Met Lys Ile Pro His Gln Thr Gln Lys Lys Arg Ser Leu Glu Asp 10 Pro Asn Ser Arg Pro Arg Arg Pro Arg Gly Glu Gly Glu Thr Trp Gly 20 25 Arg Val Thr Met Thr Lys Leu Ala Gln Trp Leu Trp Gly Leu Ala Ile 45 40 Leu Gly Ser Thr Trp Val Ala Leu Thr Thr Gly Ala Leu Gly Leu Glu 55 Leu Pro Leu Ser Cys Gln Glu Val Leu Trp Pro Leu Pro Ala Tyr Leu 75 70 Leu Val Ser Ala Gly Cys Tyr Ala Leu Gly Thr Val Gly Tyr Arg Val 90 85 Ala Thr Phe His Asp Cys Glu Asp Ala Ala Arg Glu Leu Gln Ser Gln 105 100

Val Ser Thr Phe Ile Lys Cys Leu Ala Leu Lys Ser Ile Ile Lys Arg
35 40 45

Gln Arg Ser Glu Ile Asn Arg Gly Phe Leu Ala Ile Tyr His Ala Leu
50 55 60

Arg Asn Gln Val Thr Arg Cys Gly Gly Leu \*

<210> 265 <211> 71 <212> PRT <213> Homo sapiens

<400> 265

<210> 266 <211> 53 <212> PRT <213> Homo sapiens

<400> 266

 Met Phe Thr His Trp Leu Gly Pro Pro Val Tyr Ile Lys Gln Phe Ile
 1
 15

 Val Met Ile Val Ser Ile Leu Thr Leu Phe Pro Val Leu Gln Gly Met
 20
 25
 30

 Leu Arg Asn Phe Leu Tyr Leu Asn Ile Met Phe Val Val Ala Leu Leu
 35
 40
 45

 Lys Ala Ile Leu \*
 50
 52
 50
 52

<210> 267 <211> 203 <212> PRT <213> Homo sapiens

<400> 267

Met Glu Arg Gly Ala Gly Ala Lys Leu Leu Pro Leu Leu Leu Leu Leu Leu Leu 15

Arg Ala Thr Gly Phe Thr Cys Ala Gln Ala Asp Gly Arg Asn Gly Tyr
20

Thr Ala Val Ile Glu Val Thr Ser Gly Gly Pro Trp Gly Asp Trp Ala
35

Trp Pro Glu Met Cys Pro Asp Gly Phe Phe Ala Ser Gly Pro Trp Gly Asp Ceu
50

Lys Val Glu Pro Pro Gln Gly Ile Pro Gly Asp Asp Thr Ala Leu Asn
65

<210> 262 <211> 65 <212> PRT <213> Homo sapiens

<210> 263 <211> 71 <212> PRT <213> Homo sapiens

<210> 264 <211> 75 <212> PRT <213> Homo sapiens

<210> 259 <211> 65 <212> PRT <213> Homo sapiens

<400> 259

 Met
 Lys
 Pro
 Tyr
 Cys
 Met
 Tyr
 Pro
 Phe
 Leu
 Ser
 Gly
 Leu
 Ser
 15

 Leu
 Leu
 Phe
 Trp
 Leu
 Glu
 Ser
 Leu
 Met
 Leu
 Cys
 Val
 Gln
 Met
 Val

 Leu
 Phe
 Leu
 Met
 Leu
 Asp
 Tyr
 Arg
 Ile
 Tyr
 Cys
 Ile
 Lys

 Je
 Tyr
 Val
 Ser
 Ile
 Leu
 Met
 Ser
 Ile
 Tyr
 Cys
 Ile
 Lys

 Je
 Tyr
 Val
 Leu
 Leu
 Met
 Ser
 Ile
 Tyr
 Cys
 Ile
 Lys

 Je
 Tyr
 Val
 Leu
 Met
 Ser
 Ile
 Tyr
 Lys
 Lys

 Je
 Tyr
 Val
 Leu
 Met
 Ser
 Ile
 Tyr
 Lys
 Lys
 Lys

 Je
 Tyr</t

<210> 260 <211> 65 <212> PRT <213> Homo sapiens

<210> 261 <211> 193 <212> PRT <213> Homo sapiens

<400> 261 Met Leu Met Tyr Arg Gly Glu Ala Leu Glu Asp Phe Thr Gly Pro Asp 10 Cys Arg Phe Val Asn Phe Lys Lys Gly Asp Pro Val Tyr Val Tyr 20 25 Lys Leu Ala Arg Gly Trp Pro Glu Val Trp Ala Gly Ser Val Gly Arg 35 40 Thr Phe Gly Tyr Phe Pro Lys Asp Leu Ile Gln Val Val His Glu Tyr 55 60 Thr Lys Glu Glu Leu Gln Val Pro Thr Asp Glu Thr Asp Phe Val Cys 70 75 Phe Asp Gly Gly Arg Asp Asp Phe His Asn Tyr Asn Val Glu Glu Leu 85 90 Leu Gly Phe Leu Glu Leu Tyr Asn Ser Ala Ala Thr Asp Ser Glu Lys 100 105 Ala Val Glu Gln Thr Leu Gln Asp Met Glu Lys Asn Pro Glu Leu Ser 120

Leu Lys Ala His Val Gln Ile Val Leu Tyr Trp Val Phe Leu Trp Ser

35 40 45

Arg Gly Asn Asn Phe Leu Thr

50 55

<210> 256 <211> 52 <212> PRT <213> Homo sapiens

<210> 257 <211> 55 <212> PRT <213> Homo sapiens

<210> 258 <211> 86 <212> PRT <213> Homo sapiens

<400> 258 Met Trp Pro Gly Cys Gln Val Leu Arg Ala Gly Leu Ser Pro Ala Gly 10 Arg Ala Arg Phe Pro Pro Asp Thr Tyr Leu Pro Ser Pro Arg Gln Gly 20 25 30 Gly Asn Pro Ala Cys Arg Cys Val Thr Ala Met Asn Ala Val Leu Gln 35 40 45 Val Leu Pro His Pro Ala Pro Asp Thr Asn Arg Ala Asp Glu Gly Cys 55 60 Gly Asp Gln Glu Gly Ser Arg Glu Leu Pro Pro Gly Gly Ala Ala Leu Gly His Arg Gly Gln 85

<213> Homo sapiens

<400> 252 Met Glu Thr Asp Pro Ala Ser Trp Pro Gln Pro Glu Pro Ala Gln Leu 10 Pro Gly Leu Tyr Ala Asp Phe Arg Ser Arg Thr Pro Arg Asp Ala Pro 20 25 30 Ala Gly Cys Pro Arg Trp Gly Trp Arg Cys Leu Ser Ala Ala Gln Pro 40 45 Ser Thr Gly Arg Thr Gly Glu Gly Ala Gly Pro Pro Gly Leu Cys Ala 55 Asp Gln Pro Cys Gly Ala Ala Ala Gly Gly Gly Ala Glu Lys Gln 70 Pro Ala Arg Ala Cys Gly Gly Asp Cys Trp Gly Gly Pro Met Pro His 85 90 Gly Arg Glu Pro Glu Ser Gly Ser Ala Ala Lys Val Ser Val Cys Pro Gly Glu Glu \* 115

<210> 253 <211> 27 <212> PRT

<213> Homo sapiens

<210> 254 <211> 44 <212> PRT <213> Homo sapiens

<210> 255 <211> 55 <212> PRT <213> Homo sapiens

 $^{<400>}$  255 Met Tyr Met Asn Thr Cys Leu Tyr Leu His Val Tyr Val Leu Thr Cys 1  $^{5}$  5  $^{10}$  6  $^{10}$  6  $^{15}$  5 Ser Gly Cys Asn Val Asp Met Cys Ser Arg Leu Phe Leu Ser Thr Lys  $^{20}$ 

Gly Glu Ser Val Thr Ala Met Glu Leu Glu Phe Lys Leu Leu Ala Ser 1635 1640 1645 Ser Lys Ala His Thr Ser Arg Phe Ile Ser Ala Asn Leu Pro Cys Asn 1650 1655 1660 Lys Phe Lys Asn Arg Leu Val Asn Ile Met Pro Tyr Glu Leu Thr Arg 1665 1670 1675 1680 Val Cys Leu Gln Pro Ile Arg Gly Val Glu Gly Ser Asp Tyr Ile Asn 1685 1690 1695 Ala Ser Phe Leu Asp Gly Tyr Arg Gln Gln Lys Ala Tyr Ile Ala Thr 1700 1705 1710 Gln Gly Pro Leu Ala Glu Ser Thr Glu Asp Phe Trp Arg Met Leu Trp 1715 1720 1725 Glu His Asn Ser Thr Ile Ile Val Met Leu Thr Lys Leu Arg Glu Met 1730 1735 1740 Gly Arg Glu Lys Cys His Gln Tyr Trp Pro Ala Glu Arg Ser Ala Arg 1745 1750 1755 1760 Tyr Gln Tyr Phe Val Val Asp Pro Met Ala Glu Tyr Asn Met Pro Gln 1765 1770 1775 Tyr Ile Leu Arg Glu Phe Lys Val Thr Asp Ala Arg Asp Gly Gln Ser 1780 1785 1790 Arg Thr Ile Arg Gln Phe Gln Phe Thr Asp Trp Pro Glu Gln Gly Val 1795 1800 1805 Pro Lys Thr Gly Glu Gly Phe Ile Asp Phe Ile Gly Gln Val His Lys 1810 1815 1820 Thr Lys Glu Gln Phe Gly Gln Asp Gly Pro Ile Thr Val His Cys Ser 1825 1830 1835 1840 Ala Gly Val Gly Arg Thr Gly Val Phe Ile Thr Leu Ser Ile Val Leu 1845 1850 1855 Glu Arg Met Arg Tyr Glu Gly Val Val Asp Met Phe Gln Thr Val Lys 1860 1865 1870 Thr Leu Arg Thr Gln Arg Pro Ala Met Val Gln Thr Glu Asp Gln Tyr 1875 1880 1885 Gln Leu Cys Tyr Arg Ala Ala Leu Glu Tyr Leu Gly Ser Phe Asp His 1890 1895 1900 Tyr Ala Thr 1905 1907

<210> 251

<211> 94

<212> PRT

<213> Homo sapiens

<400> 251

Met Ile Trp Ile Tyr Phe Ala Phe Ile Phe Gln Arg Leu His Leu Ile 1 5 10 Pro Gly Lys Ser Ser Ala Arg Gln Val Ser Gly Phe Ser Leu Leu Ser 20 25 30 Phe Asn Pro Ser Asn Thr Ile Phe Val Lys Leu Asp Trp Trp Cys Phe 35 40 45 Ile Gln Leu Ile Tyr Ser Ala Tyr Leu Phe Glu Lys Arg Leu Leu Glu 50 55 60 Ile Asp Asp Val Phe Val Pro Val Ile Leu Lys Val Val Gly Ala Arg 70 - 75 Ile Glu Phe His Ser Gly Ile Gly Phe Gly Ser Gly Leu 85 90

<210> 252

<211> 116

<212> PRT

Pro His Val Gln Asp Pro Ser Leu Val Arg Trp Phe Tyr Ile Val Val 1125 1130 Val Pro Ile Asp Arg Val Gly Gly Ser Met Leu Thr Pro Arg Trp Ser 1140 1145 1150 Thr Pro Glu Glu Leu Glu Leu Asp Glu Leu Leu Glu Ala Ile Glu Gln 1155 1160 1165 Gly Glu Glu Gln Arg Arg Arg Arg Gln Ala Glu Arg Leu Lys 1175 1180 Pro Tyr Val Ala Ala Gln Leu Asp Val Leu Pro Glu Thr Phe Thr Leu 1190 1195 1200 Gly Asp Lys Lys Asn Tyr Arg Gly Phe Tyr Asn Arg Pro Leu Ser Pro 1205 1210 1215 Asp Leu Ser Tyr Gln Cys Phe Val Leu Ala Ser Leu Lys Glu Pro Met 1225 1220 1230 Asp Gln Lys Arg Tyr Ala Ser Ser Pro Tyr Ser Asp Glu Ile Val Val 1235 1240 1245 Gln Val Thr Pro Ala Gln Gln Glu Glu Pro Glu Met Leu Trp Val 1250 1255 1260 Thr Gly Pro Val Leu Ala Val Ile Leu Ile Ile Leu Ile Val Ile Ala 1270 1275 1280 Ile Leu Leu Phe Lys Arg Lys Arg Thr His Ser Pro Ser Ser Lys Asp 1285 1290 1295 Glu Gln Ser Ile Gly Leu Lys Asp Ser Leu Leu Ala His Ser Ser Asp 1300 1305 Pro Val Glu Met Arg Arg Leu Asn Tyr Gln Thr Pro Gly Met Arg Asp 1315 1320 1325 His Pro Pro Ile Pro Ile Thr Asp Leu Ala Asp Asn Ile Glu Arg Leu 1335 1340 Lys Ala Asn Asp Gly Leu Lys Phe Ser Gln Glu Tyr Glu Ser Ile Asp 1350 1355 Pro Gly Gln Gln Phe Thr Trp Glu Asn Ser Asn Leu Glu Val Asn Lys 1365 1370 1375 Pro Lys Asn Arg Tyr Ala Asn Val Ile Ala Tyr Asp His Ser Arg Val 1380 1385 1390 Ile Leu Thr Ser Ile Asp Gly Val Pro Gly Ser Asp Tyr Ile Asn Ala 1395 1400 1405 Asn Tyr Ile Asp Gly Tyr Arg Lys Gln Asn Ala Tyr Ile Ala Thr Gln 1415 1420 Gly Pro Leu Pro Glu Thr Met Gly Asp Phe Trp Arg Met Val Trp Glu 1425 1430 1435 1440 Gln Arg Thr Ala Thr Val Val Met Met Thr Arg Leu Glu Glu Lys Ser 1450 1445 1455 Arg Val Lys Cys Asp Gln Tyr Trp Pro Ala Arg Gly Thr Glu Thr Cys 1460 1465 1470 Gly Leu Ile Gln Val Thr Leu Leu Asp Thr Val Glu Leu Ala Thr Tyr 1475 1480 1485 Thr Val Arg Thr Phe Ala Leu His Lys Ser Gly Ser Ser Glu Lys Arg 1495 1500 Glu Leu Arg Gln Phe Gln Phe Met Ala Trp Pro Asp His Gly Val Pro 1510 1515 Glu Tyr Pro Thr Pro Ile Leu Ala Phe Leu Arg Arg Val Lys Ala Cys 1525 1530 Asn Pro Leu Asp Ala Gly Pro Met Val Val His Cys Ser Ala Gly Val 1540 1545 1550 Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ala Met Leu Glu Arg Met 1560 1565 Lys His Glu Lys Thr Val Asp Ile Tyr Gly His Val Thr Cys Met Arg 1575 1580 Ser Gln Arg Asn Tyr Met Val Gln Thr Glu Asp Gln Tyr Val Phe Ile 1585 1590 1595 His Glu Ala Leu Leu Glu Ala Ala Thr Cys Gly His Thr Glu Val Pro 1605 1610 1615 Ala Arg Asn Leu Tyr Ala His Ile Gln Lys Leu Gly Gln Val Pro Pro 1620 1625

Pro Pro Gln Lys Val Met Cys Val Ser Met Gly Ser Thr Thr Val Arg 615 Val Ser Trp Val Pro Pro Ala Asp Ser Arg Asn Gly Val Ile Thr 630 635 Gln Tyr Ser Val Ala Tyr Glu Ala Val Asp Gly Glu Asp Arg Gly Arg 645 650 His Val Val Asp Gly Ile Ser Arg Glu His Ser Ser Trp Asp Leu Val Gly Leu Glu Lys Trp Thr Glu Tyr Arg Val Trp Val Arg Ala His Thr 680 685 Asp Val Gly Pro Gly Pro Glu Ser Ser Pro Val Leu Val Arg Thr Asp 700 695 Glu Asp Val Pro Ser Gly Pro Pro Arg Lys Val Glu Val Glu Pro Leu . 715 710 Asn Ser Thr Ala Val His Val Tyr Trp Lys Leu Pro Val Pro Ser Lys 730 725 Gln His Gly Gln Ile Arg Gly Tyr Gln Val Thr Tyr Val Arg Leu Glu 740 745 Asn Gly Glu Pro Arg Gly Leu Pro Ile Ile Gln Asp Val Met Leu Ala 765 755 760 Glu Ala Gln Trp Arg Pro Glu Glu Ser Glu Asp Tyr Glu Thr Thr Ile 770 775 780 Ser Gly Leu Thr Pro Glu Thr Thr Tyr Ser Val Thr Val Ala Ala Tyr 790 795 Thr Thr Lys Gly Asp Gly Ala Arg Ser Lys Pro Lys Ile Val Thr Thr 805 810 Thr Gly Ala Val Pro Gly Arg Pro Thr Met Met Ile Ser Thr Thr Ala 820 825 830 Met Asn Thr Ala Leu Leu Gln Trp His Pro Pro Lys Glu Leu Pro Gly 835 840 845 Glu Leu Leu Gly Tyr Arg Leu Gln Tyr Cys Arg Ala Asp Glu Ala Arg 855 860 Pro Asn Thr Ile Asp Phe Gly Lys Asp Asp Gln His Phe Thr Val Thr 870 875 Gly Leu His Lys Gly Thr Thr Tyr Ile Phe Arg Leu Ala Ala Lys Asn 890 Arg Ala Gly Leu Gly Glu Glu Phe Glu Lys Glu Ile Arg Thr Pro Glu 905 Asp Leu Pro Ser Gly Phe Pro Gln Asn Leu His Val Thr Gly Leu Thr 915 920 925 Thr Ser Thr Thr Glu Leu Ala Trp Asp Pro Pro Val Leu Ala Glu Arg 940 935 Asn Gly Arg Ile Ile Ser Tyr Thr Val Val Phe Arg Asp Ile Asn Ser 950 955 Gln Gln Glu Leu Gln Asn Ile Thr Thr Asp Thr Arg Phe Thr Leu Thr 965 970 Gly Leu Lys Pro Asp Thr Thr Tyr Asp Ile Lys Val Arg Ala Trp Thr 985 Ser Lys Gly Ser Gly Pro Leu Ser Pro Ser Ile Gln Ser Arg Thr Met 995 1000 1005 Pro Val Glu Gln Val Phe Ala Lys Asn Phe Arg Val Ala Ala Met 1010 1015 1020 Lys Thr Ser Val Leu Leu Ser Trp Glu Val Pro Asp Ser Tyr Lys Ser 1030 1035 Ala Val Pro Phe Lys Ile Leu Tyr Asn Gly Gln Ser Val Glu Val Asp 1045 1050 1055 Gly His Ser Met Arg Lys Leu Ile Ala Asp Leu Gln Pro Asn Thr Glu 1060 1065 1070 Tyr Ser Phe Val Leu Met Asn Arg Gly Ser Ser Ala Gly Gly Leu Gln 1080 1085 His Leu Val Ser Ile Arg Thr Ala Pro Asp Leu Leu Pro His Lys Pro 1095 1100 Leu Pro Ala Ser Ala Tyr Ile Glu Asp Gly Arg Phe Asp Leu Ser Met 1110 1115

Arg Val Gln Arg Asp Glu Ala Ile Tyr Glu Cys Thr Ala Thr Asn Ser Leu Gly Glu Ile Asn Thr Ser Ala Lys Leu Ser Val Leu Glu Glu Glu Gln Leu Pro Pro Gly Phe Pro Ser Ile Asp Met Gly Pro Gln Leu Lys Val Val Glu Lys Ala Arg Thr Ala Thr Met Leu Cys Ala Ala Gly Gly Asn Pro Asp Pro Glu Ile Ser Trp Phe Lys Asp Phe Leu Pro Val Asp Pro Ala Thr Ser Asn Gly Arg Ile Lys Gln Leu Arg Ser Gly Ala Leu Gln Ile Glu Ser Ser Glu Glu Ser Asp Gln Gly Lys Tyr Glu Cys Val Ala Thr Asn Ser Ala Gly Thr Arg Tyr Ser Ala Pro Ala Asn Leu Tyr Val Arg Val Arg Val Ala Pro Arg Phe Ser Ile Pro Pro Ser Ser Gln Glu Val Met Pro Gly Gly Ser Val Asn Leu Thr Cys Val Ala Val Gly Ala Pro Met Pro Tyr Val Lys Trp Met Met Gly Ala Glu Glu Leu Thr Lys Glu Asp Glu Met Pro Val Gly Arg Asn Val Leu Glu Leu Ser Asn Val Val Arg Ser Ala Asn Tyr Thr Cys Val Ala Ile Ser Ser Leu Gly Met Ile Glu Ala Thr Ala Gln Val Thr Val Lys Ala Leu Pro Lys Pro Pro Ile Asp Leu Val Val Thr Glu Thr Thr Ala Thr Ser Val Thr Leu Thr Trp Asp Ser Gly Asn Ser Glu Pro Val Thr Tyr Tyr Gly Ile Gln Tyr Arg Ala Ala Gly Thr Glu Gly Pro Phe Gln Glu Val Asp Gly Val Ala Thr Thr Arg Tyr Ser Ile Gly Gly Leu Ser Pro Phe Ser Glu Tyr Ala Phe Arg Val Leu Ala Val Asn Ser Ile Gly Arg Gly Pro Pro Ser Glu Ala Val Arg Ala Arg Thr Gly Glu Gln Ala Pro Ser Ser Pro Pro Arg Arg Val Gln Ala Arg Met Leu Ser Ala Ser Thr Met Leu Val Gln Trp Glu Pro Pro Glu Glu Pro Asn Gly Leu Val Arg Gly Tyr Arg Val Tyr Tyr Thr Pro Asp Ser Arg Arg Pro Pro Asn Ala Trp His Lys His Asn Thr Asp Ala Gly Leu Leu Thr Thr Val Gly Ser Leu Leu Pro Gly Ile Thr Tyr Ser Leu Arg Val Leu Ala Phe Thr Ala Val Gly Asp . Gly Pro Pro Ser Pro Thr Ile Gln Val Lys Thr Gln Gln Gly Val Pro Ala Gln Pro Ala Asp Phe Gln Ala Glu Val Glu Ser Asp Thr Arg Ile Gln Leu Ser Trp Leu Leu Pro Pro Gln Glu Arg Ile Ile Met Tyr Glu Leu Val Tyr Trp Ala Ala Glu Asp Glu Asp Gln Gln His Lys Val Thr Phe Asp Pro Thr Ser Ser Tyr Thr Leu Glu Asp Leu Lys Pro Asp Thr Leu Tyr Arg Phe Gln Leu Ala Ala Arg Ser Asp Met Gly Val Gly Val Phe Thr Pro Thr Ile Glu Ala Arg Thr Ala Gln Ser Thr Pro Ser Ala . 605

Thr Phe Trp Phe Asn Met Ala Asp Ala Ala Phe Gln Ser Leu Val Cys 870 875 Phe Ser Ile Pro Tyr Leu Ala Tyr Tyr Asp Ser Asn Val Asp Leu Phe 885 890 Thr Trp Gly Thr Pro Ile Val Thr Ile Ala Leu Leu Thr Phe Leu Leu 905 His Leu Gly Ile Glu Thr Lys Thr Trp Thr Trp Leu Asn Trp Ile Thr 915 920 925 Cys Gly Phe Ser Val Leu Leu Phe Phe Thr Val Ala Leu Ile Tyr Asn 930 935 940 Ala Ser Cys Ala Thr Cys Tyr Pro Pro Ser Asn Pro Tyr Trp Thr Met 950 955 Gln Ala Leu Leu Gly Asp Pro Val Phe Tyr Leu Thr Cys Leu Met Thr 965 970 Pro Val Ala Ala Leu Leu Pro Arg Leu Phe Phe Arg Ser Leu Gln Gly 980 985 990 Arg Val Phe Pro Thr Gln Leu Gln Leu Ala Arg Gln Leu Thr Arg Lys 995 1000 1005 Ser Pro Arg Arg Cys Ser Ala Pro Lys Glu Thr Phe Ala Gln Gly Arg 1010 1015 1020 Leu Pro Lys Asp Ser Gly Thr Glu His Ser Ser Gly Arg Thr Val Lys 1030 1035 Thr Ser Val Pro Leu Ser Gln Pro Ser Trp His Thr Gln Gln Pro Val 1045 1050 1055 Cys Ser Leu Glu Ala Ser Gly Glu Pro Ser Thr Val Asp Met Ser Met 1060 1065 1070 Pro Val Arg Glu His Thr Leu Leu Glu Gly Leu Ser Ala Pro Ala Pro 1075 1080 1085 Met Ser Ser Ala Pro Gly Glu Ala Val Leu Arg Ser Pro Gly Gly Cys 1090 1095 1100 Pro Glu Glu Ser Lys Val Arg Ala Ala Ser Thr Gly Arg Val Thr Pro 1105 1110 1115 1120 Leu Ser Ser Leu Phe Ser Leu Pro Thr Phe Ser Leu Leu Asn Trp Ile 1125 1130 1135 Ser Ser Trp Ser Leu Val Ser Arg Leu Gly Ser Val Leu Gln Phe Ser 1140 1145 1150 Arg Thr Glu Gln Leu Ala Asp Gly Gln Ala Gly Arg Gly Leu Pro Val 1155 1160 1165 Gln Pro His Ser Gly Arg Ser Gly Leu Gln Gly Pro Asp His Arg Leu 1170 1175 Leu Ile Gly Ala Ser Ser Arg Arg Ser Gln \* 1190 1194

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Leu Gly Gln Pro Thr Ser Ala Ile Ala Ser Asn Gly Tyr Ser Ser Gln Ala Asp Asn Trp Ala Ser Glu Leu Ala Gln Glu Gln Glu Ser Glu Arg Glu Leu Arg Tyr Glu Ala Glu Ser Pro Asp Glu Ala Ala Leu Val Tyr 3.90 Ala Ala Arg Ala Tyr Asn Cys Val Leu Val Glu Arg Leu His Asp Gln Val Ser Val Glu Leu Pro His Leu Gly Arg Leu Thr Phe Glu Leu Leu His Thr Leu Gly Phe Asp Ser Val Arg Lys Arg Met Ser Val Val Ile Arg His Pro Leu Thr Asp Glu Ile Asn Val Tyr Thr Lys Gly Ala Asp Ser Val Val Met Asp Leu Leu Gln Pro Cys Ser Ser Val Asp Ala Arg Gly Arg His Gln Lys Lys Ile Arg Ser Lys Thr Gln Asn Tyr Leu Asn Val Tyr Ala Ala Glu Gly Leu Arg Thr Leu Cys Ile Ala Lys Arg Val Leu Ser Lys Glu Glu Tyr Ala Cys Trp Leu Gln Ser His Leu Glu Ala Glu Ser Ser Leu Glu Asn Ser Glu Glu Leu Leu Phe Gln Ser Ala Ile Arg Leu Glu Thr Asn Leu His Leu Leu Gly Ala Thr Gly Ile Glu Asp Arg Leu Gln Asp Gly Val Pro Glu Thr Ile Ser Lys Leu Arg Gln Ala Gly Leu Gln Ile Trp Val Leu Thr Gly Asp Lys Gln Glu Thr Ala Val Asn Ile Ala Tyr Ala Cys Lys Leu Leu Asp His Asp Glu Glu Val Ile Thr Leu Asn Ala Thr Ser Gln Glu Ala Cys Ala Ala Leu Leu Asp Gln Cys Leu Cys Tyr Val Gln Ser Arg Gly Pro Gln Arg Ala Pro Glu Lys Thr Lys Gly Lys Val Ser Met Arg Phe Ser Ser Leu Cys Pro Pro Ser Thr Ser Thr Ala Ser Gly Arg Arg Pro Ser Leu Val Ile Asp Gly Arg Ser Leu Ala Tyr Ala Leu Glu Lys Asn Leu Glu Asp Lys Phe Leu Phe Leu Ala Lys Gln Cys Arg Ser Val Leu Cys Cys Arg Ser Thr Pro Leu Gln Lys Ser Met Val Val Lys Leu Val Arg Ser Lys Leu Lys Ala Met Thr Leu Ala Ile Gly Asp Gly Ala Asn Asp Val Ser Met Ile Gln Val Ala Asp Val Gly Val Gly Ile Ser Gly Gln Glu Gly Met Gln Ala Val Met Ala Ser Asp Phe Ala Val Pro Lys Phe Arg Tyr Leu Glu Arg Leu Leu Ile Leu His Gly His Trp Cys Tyr Ser Arg Leu Ala Asn Met Val Leu Tyr Phe Phe Tyr Lys Asn Thr Met Phe Val Gly Leu Leu Phe Trp Phe Gln Phe Phe Cys Gly Phe Ser Ala Ser Thr Met Ile Asp Gln Trp Tyr Leu Ile Phe Phe Asn Leu Leu Phe Ser Ser Leu Pro Pro Leu Val Thr Gly Val Leu Asp Arg Asp Val Pro Ala Asn Val Leu Leu Thr Asn Pro Gln Leu Tyr Lys Ser Gly Gln Asn Met Glu Glu Tyr Arg Pro Arg 

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Gly Ser Thr Ala Leu Lys Ala Glu Thr Ser Glu Arg Leu Arg Thr Val Leu Leu Asp Val Thr Asp Pro Glu Asn Val Lys Arg Thr Ala Gln Trp Val Lys Asn Gln Val Gly Glu Lys Gly Leu Trp Gly Leu Ile Asn Asn Ala Gly Val Pro Gly Val Leu Ala Pro Thr Asp Trp Leu Thr Leu Glu Asp Tyr Arg Glu Pro Ile Glu Val Asn Leu Phe Gly Leu Ile Ser Val Thr Leu Asn Met Leu Pro Leu Val Lys Lys Ala Gln Gly Arg Val Ile Asn Val Ser Ser Val Gly Gly Arg Leu Ala Ile Val Gly Gly Tyr Thr Pro Ser Lys Tyr Ala Val Glu Gly Phe Asn Asp Ser Leu Arg Arg Asp Met Lys Ala Phe Gly Val His Val Ser Cys Ile Glu Pro Gly Leu Phe Lys Thr Asn Leu Ala Asp Pro Val Lys Val Ile Glu Lys Lys Leu Ala Ile Trp Glu Gln Leu Ser Pro Asp Ile Lys Gln Gln Tyr Gly Glu Gly Tyr Ile Glu Lys Ser Leu Asp Lys Leu Lys Gly Asn Lys Ser Tyr Val Asn Met Asp Leu Ser Pro Val Val Glu Cys Met Asp His Ala Leu Thr Ser Leu Phe Pro Lys Thr His Tyr Ala Ala Gly Lys Asp Ala Lys Ile Phe Trp Ile Pro Leu Ser His Met Pro Ala Ala Leu Gln Asp Phe Leu Leu Lys Gln Lys Ala Glu Leu Ala Asn Pro Lys Ala Val \* 

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Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 40 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 60 Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 70 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp 90 95 85 Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His · 105 100 110 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Glu Gly Lys Ile 120 125 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 135 140 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 150 155 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 165 170 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 185 190 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala 195 200 205 Pro Arg Gly Arg Ala Ser Glu Pro Lys His Lys Thr Arg Gln Arg \* 215 220

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20 25 30

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Gly Glu Pro Gly Pro Val Gly Val Gln Gly Pro Pro Gly Pro Ala Gly Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Thr Gly Leu Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly Ala Asp Gly Ser Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ser Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala Gly Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly Pro Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu Gly Gly Lys Gly Pro Arg Gly Glu Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val . 955

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440

Gln Val Gly Tyr Gly Met Ala Ala Gly Tyr Thr Ile Phe Ile Thr Ser 215 220 Phe Leu Gly Val Leu Val Phe Ser Arg Cys Phe Arg Asp Thr Thr Met 230 235 Ile Met Ile Gly Met Val Ser Phe Gly Ser Gly Ala Leu Leu Leu Ala 245 250 Phe Val Lys Glu Thr Tyr Met Phe Tyr Ile Ala Arg Ala Val Met Leu 265 Phe Ala Leu Ile Pro Val Thr Thr Ile Arg Ser Ala Met Ser Lys Leu 275 280 285 Ile Lys Gly Ser Ser Tyr Gly Lys Val Phe Val Ile Leu Gln Leu Ser 290 295 300 Leu Ala Leu Thr Gly Val Val Thr Ser Thr Leu Tyr Asn Lys Ile Tyr 310 315 Gln Leu Thr Met Asp Met Phe Val Gly Ser Cys Phe Ala Leu Ser Ser 325 330 335 Phe Leu Ser Phe Leu Ala Ile Ile Pro Ile Ser Ile Val Ala Tyr Lys 340 345 Gln Val Pro Leu Ser Pro Tyr Gly Asp Ile Ile Glu Lys \* 360

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Arg Tyr Arg Ile Leu Leu Val Thr Val Leu Trp Thr Leu Leu Val Tyr 340 345 Ser Met Leu Ser His Lys Glu Phe Arg Phe Ile Tyr Pro Val Leu Pro 360 Phe Cys Met Val Phe Cys Gly Tyr Ser Leu Thr His Leu Lys Thr Trp 375 380 Lys Lys Pro Ala Leu Ser Phe Leu Phe Leu Ser Asn Leu Phe Leu Ala 390 395 Leu Tyr Thr Gly Leu Val His Gln Arg Gly Thr Leu Asp Val Met Ser 405 410 His Ile Gln Lys Val Cys Tyr Asn Asn Pro Asn Lys Ser Ser Ala Ser 420 425 430 Ile Phe Ile Met Met Pro Cys His Ser Thr Pro Tyr Tyr Ser His Val 435 440 His Cys Pro Leu Pro Met Arg Phe Leu Gln Cys Pro Pro Asp Leu Thr 450 455 460 Gly Lys Ser His Tyr Leu Asp Glu Ala Asp Val Phe Tyr Leu Asn Pro 465 470 475 Leu Asn Trp Leu His Arg Glu Phe His Asp Asp Ala Ser Leu Pro Thr 485 490 His Leu Ile Thr Phe Ser Ile Leu Glu Glu Glu Ile Ser Ala Phe Leu 500 505 Ile Ser Ser Asn Tyr Lys Arg Thr Ala Val Phe Phe His Thr His Leu 515 520 525 Pro Glu Gly Arg Ile Gly Ser His Ile Tyr Val Tyr Glu Arg Lys Leu 535 Lys Gly Lys Phe Asn Met Lys Met Lys Phe 545 550

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<400> 241

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Leu Arg Asp Ala Asp Asp Leu Gln Lys Arg Leu Ala Val Tyr Gln Ala 200 Gly Ala Arg Glu Gly Ala Glu Arg Gly Leu Ser Ala Ile Arg Glu Arg 215 220 Leu Gly Pro Leu Val Glu Gln Gly Pro Arg Ala Gly Arg His Cys Gly 230 235 Leu Pro Gly Pro Ala Ser Arg Tyr Arg Ser Gly Pro Arg Pro Gly Ala 245 250 Ser Gly Cys Ala Arg Gly Trp Arg Arg Trp Ala Ala Gly Pro Ala Thr 260 265 Ala Trp Thr Arg 275 276

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Ala Lys Val Leu Glu Arg Gly Lys Asp Ala Thr Leu Gln Lys Gln Glu Asp Val Ala Val Ala Ala Val Leu Glu Ser Leu Leu Lys Leu Ala Leu Leu Ala Gly Leu Thr Ile Thr Val Phe Gly Phe Ala Tyr Ser Gln Leu Ala Leu Asp Ile Tyr Gly Gly Thr Met Leu Ser Ser Gly Ser Gly Pro Val Leu Leu Arg Ser Tyr Cys Leu Tyr Val Leu Leu Leu Ala Ile Asn Gly Val Thr Glu Cys Phe Thr Phe Ala Ala Met Ser Lys Glu Glu Val Asp Arg Tyr Asn Phe Val Met Leu Ala Leu Ser Ser Ser Phe Leu Val Leu Ser Tyr Leu Leu Thr Arg Trp Cys Gly Ser Val Gly Phe Ile Leu Ala Asn Cys Phe Asn Met Gly Ile Arg Ile Thr Gln Ser Leu Cys Phe Ile His Arg Tyr Tyr Arg Arg Ser Pro His Arg Pro Leu Ala Gly Leu His Leu Ser Pro Val Leu Leu Gly Thr Phe Ala Leu Ser Gly Gly Val Thr Ala Val Ser Glu Val Phe Leu Cys Cys Glu Gln Gly Trp Pro Ala Arg Leu Ala His Ile Ala Val Gly Ala Phe Cys Leu Gly Ala Thr Leu Gly Thr Ala Phe Leu Thr Glu Thr Lys Leu Ile His Phe Leu Arg Thr Gln Leu Gly Val Pro Arg Arg Thr Asp Lys Met Thr \* 

<210> 239 <211> 277 <212> PRT <213> Homo sapiens

<400> 239

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Leu Arg Val Arg Leu Ala Ser His Leu Arg Lys Leu Arg Lys Arg Leu 

Lys Tyr Leu Val Lys His Cys Gly Asn Ile Pro Val Phe Val Ile Asn 360 365 Tyr Pro Leu Thr Leu Lys Pro Phe Tyr Met Arg Asp Asn Glu Asp Gly 375 380 Pro Gln His Thr Val Ala Ala Val Asp Leu Leu Val Pro Gly Val Gly 390 395 Glu Leu Phe Gly Gly Gly Leu Arg Glu Glu Arg Tyr His Phe Leu Glu 405 410 Glu Arg Leu Ala Arg Tyr Leu Asp Leu Arg Arg Phe Gly Ser Val Pro 425 420 His Gly Gly Phe Gly Met Gly Phe Glu Arg Tyr Leu Gln Cys Ile Leu 435 440 445 Gly Val Asp Asn Ile Lys Asp Val Ile Pro Phe Pro Arg Phe Pro His Ser Cys Leu Leu \* 468

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340

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Phe Thr Phe Thr Pro Glu Trp Gly Ala Asp Leu Arg Thr Glu His Glu

345

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115

110

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act gat gaa Thr Asp Glu 365				Leu								1215
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gaa aaa gat Glu Lys Asp 395	gtt aad Val Asi	aga a Arg :	aca gat Thr Asp	cga Arg	aca Thr	aac Asn 405	aag Lys	ttt Phe	tat Tyr	gaa Glu	ggc Gly 410	1311
caa gat aat Gln Asp Asn		Leu :				-		-				1359
tgt atg tat Cys Met Tyr	_	_	~~		-			_	_	_		1407
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ttg tta gac Leu Leu Asp		/ Phe (				-		_	-			1599
tac ctt tat Tyr Leu Tyr	-						_				_	1647
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cca Pro	cag Gln	gat Asp	aaa Lys 190	aga Arg	aca Thr	ctt Leu	ctt Leu	gtg Val 195	aat Asn	tgt Cys	cag Gln	aat Asn	aag Lys 200	agt Ser	ctt Leu	687
tca Ser	cag Gln	tct Ser 205	ttt Phe	gaa Glu	aat Asn	ctt Leu	ctt Leu 210	gat Asp	gag Glu	cca Pro	gca Ala	tat Tyr 215	ggt Gly	tta Leu	ata Ile	735
caa Gln	aaa Lys 220	att Ile	aaa Lys	aag Lys	gac Asp	ect Pro 225	tat Tyr	acg Thr	gca Ala	act Thr	atg Met 230	ata Ile	gga Gly	ttt Phe	tcc Ser	783
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aca Thr	cat His	caa Gln	cga Arg	cca Pro 255	cct Pro	tca Ser	gaa Glu	atg Met	gca Ala 260	gat Asp	ttt Phe	ctt Leu	agt Ser	gat Asp 265	gct Ala	879
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Cys Thr Ile Ala Thr *	418
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Leu Ser Phe Pro Lys Ala Gly Asp Phe Ser Phe Ser Ser Gln Asp Asp 15 20 25	216
15 20 25  ccc tct gag ctg aca gca gga gcc aaa gac aaa gaa ttt tct tgc ctt	216
15 20 25	
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			gag Glu													925
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Phe	Tyr	Tyr	Thr	Glu 325	Val	Gln	Leu	Lys	Glu 330	Glu	Ser	Ala	Ala	Ala 335	Ala	
	gct Ala															1174
cca Pro	gct Ala	ccc Pro 355	acc Thr	ccc Pro	agc Ser	atg Met	act Thr 360	ggc Gly	ctg Leu	cct Pro	ctg Leu	tct Ser 365	gct Ala	ctt Leu	cca Pro	1222
	cct Pro 370															1270
	tcc Ser															1318
	tgg Trp															1366
_	atc .Ile		_							-	-	_		-	-	1414
_	ccc Pro		_	_	-				_	_		-		_		1462
_	ttc Phe 450	-			_	_		_			_				-	1510
	gtc Val						-	_	-		_			-	-	1558
	gag Glu	-	-	_	_	_	_								-	1606
_	tgg Trp	_	_		_			_	_	_	_	_	_		-	1654
gac Asp	tga *	gct	gtgc	tgc a	aggti	tcta	ct c	tgtt	cctg	g cc	etge	cggc	agc	cact	gac	1710

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<220>

<221> CDS <222> (158)..(2479)

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cac His	agc Ser	tgg Trp	atg Met 100	gag Glu	ggt Gly	cag Gln	gtg Val	acc Thr 105	gtc Val	tgg Trp	ctg Leu	ctg Leu	gag Glu 110	cag Gln	aag Lys	454
ctg Leu	cag Gln	gtc Val 115	tgc Cys	tgc Cys	agg Arg	gtg Val	gag Glu 120	gag Glu	gtg Val	tgg Trp	ctg Leu	gca Ala 125	gag Glu	ctg Leu	cag Gln	502
ggc	ccc Pro 130	tgt Cys	ccc Pro	cag Gln	gca Ala	cca Pro 135	ccc Pro	ctg Leu	gag Glu	ccc Pro	gga Gly 140	gcc Ala	cag Gln	gcc Ala	ctg Leu	. 550
gcc Ala 145	tac Tyr	agg Arg	ccc Pro	gtc Val	tcc Ser 150	agg Arg	aac Asn	atc Ile	gat Asp	gtc Val 155	cca Pro	aag Lys	agg Arg	aag Lys	tcg Ser 160	598
gac Asp	gca Ala	gtg Val	gaa Glu	atg Met 165	gat Asp	gag Glu	atg Met	atg Met	gcg Ala 170	gcc Ala	atg Met	gtg Val	ctg Leu	acg Thr 175	tcc Ser	646
ctg Leu	tcc Ser	tgc Cys	agc Ser 180	cct Pro	gtt Val	gta Val	cag Gln	agt Ser 185	cct Pro	ccc Pro	Gly 999	acc Thr	gag Glu 190	gcc Ala	aac Asn	694
ttc Phe	tct Ser	gct Ala 195	tcc Ser	cgt Arg	gcg Ala	gcc Ala	tgc Cys 200	Asp	cca Pro	tgg Trp	aag Lys	gag Glu 205	agt Ser	ggt Gly	gac Asp	742
atc Ile	tcg Ser 210	Asp	agc Ser	ggc	agc Ser	agc Ser 215	act Thr	acc Thr	agc Ser	ggt Gly	cac His 220	tgg Trp	agt Ser	Gly	agc Ser	790
agt Ser 225	Gly	gtc Val	tcc Ser	acc Thr	ccc Pro 230	tcg Ser	ccc Pro	ccc Pro	cac His	ccc Pro 235	cag Gln	gcc Ala	agc Ser	ccc Pro	aag Lys 240	838
tat Tyr	ttg Leu	gly	gat Asp	gct Ala 245	ttt Phe	ggt Gly	tct Ser	ccc Pro	caa Gln 250	act Thr	gat Asp	cat His	ggc	ttt Phe 255	gag Glu	886
acc Thr	gat Asp	cct Pro	gac Asp 260	Pro	ttc Phe	ctg Leu	ctg Leu	gac Asp 265	Glu	cca Pro	gct Ala	cca Pro	cga Arg 270	Lys	aga Arg	934
aag Lys	aac Asn	Ser 275	Val	aag Lys	gtg Val	atg Met	tac Tyr 280	Lys	tgc Cys	ctg Leu	tgg Trp	cca Pro 285	Asn	tgt Cys	ggc	982
aaa Lys	gtt Val 290	Leu	cgc Arg	tcc Ser	att Ile	gtg Val 295	Gly	atc Ile	aaa Lys	cga Arg	cac His	Val	aaa Lys	gcc	ctc Leu	1030
cat His 305	Leu	ggg Gly	gac Asp	aca Thr	gtg Val 310	Asp	tct Ser	gat Asp	cag Gln	ttc Phe 315	Lys	cgg Arg	gag Glu	gag Glu	gat Asp 320	1078
tto	tac	tac	aca	gag	gtg	cag	ctg	aag	gag	gaa	tct	gct	gct	gct	gct	1126

WO 01/5543	37 245		250		PCT/US01/02623
agt gag co Ser Glu Pi	cc ttt gtg ro Phe Val 260	caa aaa ctc Gln Lys Leu	tgg gaa c Trp Glu G 265	aa tac atg gat ln Tyr Met Asp 270	gag aag 816 Glu Lys
Asp Glu Ty	ac tta cag yr Leu Gln 75	cag cta aag Gln Leu Lys 280	Gln Glu L	ett ggc ata gaa Leu Gly Ile Glu 285	ctc cat 864 Leu His
gag gaa g Glu Glu Va 290	tg act ctg al Thr Leu	ccc aag ctg Pro Lys Leu 295	cga ggg g Arg Gly G	ggc ctg atg acc Gly Leu Met Thr 300	atc gac 912 Ile Asp
ccc agc c Pro Ser L 305	tg gac aag eu Asp Lys	cag aca gtg Gln Thr Val	Asn Thr T	ac atg agc cag Tyr Met Ser Gln 315	gcc ttc 960 Ala Phe 320

cag ctc cct gag tcg gaa atg cca gag gag ggt gac gag aag gaa gaa 1008 Gln Leu Pro Glu Ser Glu Met Pro Glu Glu Gly Asp Glu Lys Glu Glu 325 330 335

gcc gtg gtg gaa atc ctc cag act gcc ctg gag cgg ctt cag gtg att 1056 Ala Val Val Glu Ile Leu Gln Thr Ala Leu Glu Arg Leu Gln Val Ile 340 345 350

gac atc agg cgt gtg gga cct cga gag cca gag cct gca agc tag 1101
Asp Ile Arg Arg Val Gly Pro Arg Glu Pro Glu Pro Ala Ser \*
355 360 365

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<220> <221> CDS

<222> (119)..(1660)

<400> 222

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358

ccc agc acc tcg ggc ctt cag cag gtg gcc ttt cag cct ggg cag aag

<pre>&lt;400&gt; 221 atg cag ctg cac atg agc acg ctg aag gaa cgg gac caa ttc ttc tct Met Gln Leu His Met Ser Thr Leu Lys Glu Arg Asp Gln Phe Phe Ser 1 5 10 15</pre>	48
gag ctg cag gag atc cag cgc act tcc acg ccg cgg cct gac tgg acc Glu Leu Gln Glu Ile Gln Arg Thr Ser Thr Pro Arg Pro Asp Trp Thr 20 25 30	96
aag tgc aaa gat gtg gtg gct ggg ggc cca gag cgc tgg cag atg ctg Lys Cys Lys Asp Val Val Ala Gly Gly Pro Glu Arg Trp Gln Met Leu 35 40 45	144
gct gag ggc aag aac agc gac cag ctg gtg gac gtg ctc ctg gaa gag Ala Glu Gly Lys Asn Ser Asp Gln Leu Val Asp Val Leu Leu Glu Glu 50 55 60	192
att ggt tcg ggg ctg ctg cgg gag aaa gac ttc ttc cct ggt ctg ggc Ile Gly Ser Gly Leu Leu Arg Glu Lys Asp Phe Phe Pro Gly Leu Gly 65 70 75 80	240
tat ggg gaa gcc atc cct gct ttt ctt cgg ttt gat ggc ctc gtg gag Tyr Gly Glu Ala Ile Pro Ala Phe Leu Arg Phe Asp Gly Leu Val Glu 85 90 95	288
aac aag aag cca agc aag gac gtg gtc aac ctc ctc aag gat gcc Asn Lys Lys Pro Ser Lys Lys Asp Val Val Asn Leu Leu Lys Asp Ala 100 105 110	336
tgg aag gaa cgt ctt gct gag gag cag aaa gag acg ttc cca gat ttc Trp Lys Glu Arg Leu Ala Glu Glu Gln Lys Glu Thr Phe Pro Asp Phe 115 120 125	384
ttc ttc aat ttc ctg gag cat cgc ttt ggg ccc agt gat gcc atg gcc Phe Phe Asn Phe Leu Glu His Arg Phe Gly Pro Ser Asp Ala Met Ala 130 135 140	432
tgg gct tat act att ttt gaa aat atc aag atc ttc cac tcc aac gag Trp Ala Tyr Thr Ile Phe Glu Asn Ile Lys Ile Phe His Ser Asn Glu 145 150 155 160	480
gtt atg agt cag ttc tat gca gtc ttg atg gga aag cgg agt gag aat Val Met Ser Gln Phe Tyr Ala Val Leu Met Gly Lys Arg Ser Glu Asn 165 170 175	528
gtg tat gtc acc cag aag gag aca gta gcc cag ctg ctg aag gag atg Val Tyr Val Thr Gln Lys Glu Thr Val Ala Gln Leu Leu Lys Glu Met 180 185 190	576
aca aat gct gac agt cag aac gag ggg cta cta acc atg gag cag ttc Thr Asn Ala Asp Ser Gln Asn Glu Gly Leu Leu Thr Met Glu Gln Phe 195 200 205	624
aac act gtc ctc aag agt acc ttc cct ctc aag aca gaa gag caa atc Asn Thr Val Leu Lys Ser Thr Phe Pro Leu Lys Thr Glu Glu Gln Ile 210 215 220	672
cag gag ctg atg gag gca ggg ggc tgg cat ccc agc agc agc aat gca Gln Glu Leu Met Glu Ala Gly Gly Trp His Pro Ser Ser Ser Asn Ala 225 230 235 240	720
gac ttg ctc aac tac cgc tca ctg ttt atg gag gat gag gag ggc cag Asp Leu Leu Asn Tyr Arg Ser Leu Phe Met Glu Asp Glu Glu Gly Gln	768

WO 01/55437 PCT/US01/0	2623
Lys Val Ile Ser Val Ile Gly Gly Leu Ala Ala Cys Phe Ile Phe Val 395 400 . 405	
ttc cca ggg ctg tgc ctc att caa gcc aaa ctc tct gag atg gaa gag Phe Pro Gly Leu Cys Leu Ile Gln Ala Lys Leu Ser Glu Met Glu Glu 410 415 420	1659
gtc aaa cca gcc agc tgg tgg gtg ctg gtc agc tac gga gtc ctc ttg Val Lys Pro Ala Ser Trp Trp Val Leu Val Ser Tyr Gly Val Leu Leu 435 430 435 440	1707
gtc acc ctg gga gcc ttc atc ttc ggc cag acc aca gcc aac gcc atc Val Thr Leu Gly Ala Phe Ile Phe Gly Gln Thr Thr Ala Asn Ala Ile 445 450 455	1755
ttt gtg gat ctc ttg gca taa cc actgcctccc agggaacaca aggcctttgc Phe Val Asp Leu Leu Ala * 460	1808
cattggtcgc aggaacccat ctcttagagc tatggggcca ttcttagtcc acgatcattc	1868
caactggtgg gatgacatcc ggacatcctc ttccagggac tggggcaaac tcaggcccca	1928
cacctctgga cagctcaaat ccagtcccct tcctgctccc cagtcctggc agtgccgtgg	1988
atggcggcag gaagteteae atcatagagg accedteete eteteecagt teteaaette	2048
tocatgootg gaatcoacgg gtgaagagag toggtagato toataagaaa gaatcoagto	2108
tgacttccct ctggagaatg actatggaca gaaggccacc atcctccaca gagcaccctg	2168
teetgagtag gggttgtget cattacecca ggccagtggt agetteetca ggageetgge	2228
cacttccaaa ggtagcactg aagtcatgca aatacatagt caggtagatt cagaccttgt	2288
ccacacette etggggcaac ecceaceatg aacetgteag ectettteec atagetaata	2348
gacatttccc aggccttgag gggccccacc ctgtctcttt catcaaacct gatggtccag	2408
gctgggcatc cctctcctcc tccatcccca gacatcacca ggtctaatgt ttacaaacgg	2468
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gttagctttc cccataaggt tgggagtatc tgcttttgtg tctgagatgg gcccctcttt	2588
tcagaggccg cagggtgggt gatggagaag gctgagaacc tttcagaccc tctgtgtggg	2648
ctgggctggt cagaatcagg gtgtacctcc ccgacacctt ctttttcagt gatgttttct	2708
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aaaaaaaaa aaaaaa	2784

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agc Ser	ggc Gly 170	cct Pro	tgg Trp	tac Tyr	aca Thr	gac Asp 175	cgc Arg	aag Lys	ttc Phe	acc Thr	atc Ile 180	agc Ser	ctc Leu	act Thr	gcc Ala	939
ttc Phe 185	ct <i>c</i> Leu	ttc Phe	atc Ile	ctg Leu	ccc Pro 190	ctc Leu	tcc Ser	atc Ile	ccc Pro	agg Arg 195	gag Glu	att Ile	ggt Gly	ttc Phe	cag Gln 200	987
aaa Lys	tat Tyr	gcc Ala	agc Ser	ttc Phe 205	ctg Leu	agc Ser	gtc Val	gtg Val	ggt Gly 210	acc Thr	tgg Trp	tac Tyr	gtc Val	aca Thr 215	gcc Ala	1035
atc Ile	gtt Val	atc Ile	atc Ile 220	aag Lys	tac Tyr	atc Ile	tgg Trp	cca Pro 225	gat Asp	aaa Lys	gag Glu	atg Met	acc Thr 230	cca Pro	Gly 999	1083
aac Asn	atc Ile	ctg Leu 235	acc Thr	agg Arg	ccg Pro	gct Ala	tcc Ser 240	tgg Trp	atg Met	gct Ala	gtg Val	ttc Phe 245	aat Asn	gcc Ala	atg Met	1131
ccc Pro	acc Thr 250	atc Ile	tgc Cys	ttc Phe	gga Gly	ttt Phe 255	cag Gln	tgc Cys	cac His	gtc Val	agc Ser 260	agt Ser	gtg Val	ccc Pro	gtc Val	1179
ttc Phe 265	aac Asn	agc Ser	atg Met	cag Gln	cag Gln 270	cct Pro	gaa Glu	gtg Val	aag Lys	acc Thr 275	tgg Trp	ggt Gly	gga Gly	gtg Val	gtg Val 280	1227
					ata Ile											1275
					ttt Phe											1323
tec Ser	tat Tyr	ccc Pro 315	Ser	gag Glu	gac Asp	atg Met	gcc Ala 320	gtg Val	gcc Ala	gtt Val	gcc Ala	cga Arg 325	gcc Ala	ttc Phe	atc Ile	1371
		Ser			acc Thr											1419
	Val				ctg Leu 350										gag Glu 360	. 1467
					gag											1515
		_			ctg Leu	_	_	-							_	1563
aag	gtg	atc	tca	gtc	att	gga	ggc	ctg	gcc	gcc	tgc	ttc	atc	ttc	gtc	1611

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ccttgcagga agaaggetet eggggee atg gee eag gte age ate aac aat	411
Met Ala Gln Val Ser Ile Asn Asn	
1 5	
	450
gac tac agc gag tgg gac ttg agc acg gat gcc ggg gag cgg gct cgg Asp Tyr Ser Glu Trp Asp Leu Ser Thr Asp Ala Gly Glu Arg Ala Arg	459
10 15 20	
ctg ctg cag agt ccc tgt gtg gac aca gcc ccc aag agt gag tgg gaa	507
Leu Leu Gln Ser Pro Cys Val Asp Thr Ala Pro Lys Ser Glu Trp Glu 25 30 35 40	
25 30 35 40	
gcc tct cct ggg ggt ctg gac aga ggc acc act tcc aca ctt ggg gcc	555
Ala Ser Pro Gly Gly Leu Asp Arg Gly Thr Thr Ser Thr Leu Gly Ala	
45 50 55	
ate tte ate gte gte aac geg tge etg ggt gea ggg tta ete aac tte	603
Ile Phe Ile Val Val Asn Ala Cys Leu Gly Ala Gly Leu Leu Asn Phe	003
60 65 70	
cca gca gcc ttc agc att gcg ggg ggc gtg gca gca ggc atc gca ctg	651
Pro Ala Ala Phe Ser Ile Ala Gly Gly Val Ala Ala Gly Ile Ala Leu 75 80 85	
7,5	
cag atg ggt atg ctg gtt ttc atc atc agt ggc ctt gtc atc ctg gcc	699
Gln Met Gly Met Leu Val Phe Ile Ile Ser Gly Leu Val Ile Leu Ala	
90 95 100	
tac tgc tcc cag gcc agc aat gag agg acc tac cag gag gtg gta tgg	747
Tyr Cys Ser Gln Ala Ser Asn Glu Arg Thr Tyr Gln Glu Val Val Trp	
105 110 115 120	
get ata tat age sea ata see agt ata ata tat acc ata acc ata act	795
gct gtg tgt ggc aag ctg aca ggt gtg cta tgt gag gtg gcc atc gct Ala Val Cys Gly Lys Leu Thr Gly Val Leu Cys Glu Val Ala Ile Ala	133
125 130 135	
	<b>.</b>
gte tae ace tit gge ace tge att gee tte eta ate ate att gge gae	843

ttaatggaaa gttgagccag aactaaacca gggagctgtc tgaaatcata gcaccccatc 3333 3393 cgggtggcgg ggagatcaac tccgagctgt ttttccgagg cagtgaggaa cggtgccggc tetgcaegga getgaggaca ggacagaeet tgetttgaga aggagetgee ggeeggggee 3453 acgetecaca geogeogege gacagtggag ceaagggtta gggcaccagg aggggecagg 3513 tggcgtcggc agcatctgtc cccagaatca ggcagaatcc acttcccaaa cagagcccca 3573 3633 cgcaggttca ccatgaacct cagggtcagg gaatgagcca ggcacggggg catgggcaga gagggccacg gggcagggcc cactgaggga acatcagtgg ccctccagtc aggttctgtg 3693 3753 ggtttggaag cccatcgtga aaggggctga cctttgcccc tttttacttg gcattggttt 3813 tgaaaccagc tgtttcccaa actctgcttc ccaagggcaa ccgttgctgt tcacacgctc 3873 agcetgtetg ggggageggg cetetagett cagecaggge gggtacacac cetgggcaca gggtcctcag cccccgggaa atgagctccc agggctggcg tcccaccttc caggtggggg 3933 ctggcacatc acagactgtc gagagcgcca tgtcccaggg catgcagagg ttgcacctag 3993 agacgttgca gcaagtggac aagtggccgc tgtgcgggcc cctcgcttgt agtgagctgt 4053 tgcagcttac ggtccgttcc ctggaggggt ggaggaagga ggtgttgggc agcatcaaag 4113 4173 qtqctqggac atcccagggt ggtgagatcc atccacgatc cagctccggt ggagaaaggg cccatgtcaa gccttgttct gcaccccaag cattggtggt aggactgggt cctggctgat 4233 cgtccttgtt cccagtgggg tacatgtgag cccctgccag ggccaagtcc ttctcccgaa 4293 cccagggtcc tgggaactgc agatcccggg gggattcagc ccttctccca ctgtgctggc 4353 agaggcactc ctgtgacgct gaatacagtg aacagggaca ttcccgccac tcggggacag 4413 atgggcacaa gggaggggaa actccatcag gaagtgctcc cctgggcaga ggcgcccact 4473 4533 gggtgctgtg ggctcaggag ggggcggggc aggagctggt gccaaccggg aaccagagcc ccacagecat acageceatt ggtgacaagg teetgagaac acagtggeca ggtgteecca 4593 ggctcctggc ccctccgacg acctcaactc tgcccagccc ggtccctggc catcagcgac 4653 getgteegee eecegteaga teceatgtgt gecatgttta teateagtgt tttgtatttt 4713 4773 tgtactgagt atcggagcac tttacagaag ctgactgtac attcctgttc tgttgtgaag agaacattcc cagaccctgg caccctcctg agccggcgtg tgccggtcca gccctccgag 4833 atgccacaat teettggatg ggggagaagt teaaggaatt tetgetegge cacgeggtgg 4893 gaaccccgcg tccccgccat gtggcagagg ggtctcagtc gtgctaggca tcgggcgca 4953 gegeegacag ceetteeete geeagtgeee eteggeeact eetgggttgg ageeegattt 5013 tatttgtaaa gttgacagtc gagcaaatgt tcctattttc gtgggatctg cacacgtctt 5073 tgtcagttgt ggtcatgatc ttagtcacct gctaattatt tttacaatga ttacaacatt 5133 tecteactge gggatattte tgaccegett tagaacttaa gacetgatte tagcaataaa 5193

wo	01/5:	5437												F	CT/US	501/02623
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gtg Val	gag Glu	cgc Arg	gag Glu	cgg Arg 445	gag Glu	cgc Arg	ctg Leu	gag Glu	ctg Leu 450	ctg Leu	cgc Arg	cgc Arg	ctc Leu	aag Lys 455	aag Lys	2597
cag Gln	aac Asn	acc Thr	gcg Ala 460	Pro	ggc Gly	gcg Ala	ctg Leu	ccg Pro 465	ccc Pro	gac Asp	aca Thr	ctg Leu	gcc Ala 470	g <u>ag</u> Glu	gcc Ala	2645
cag Gln	ccc Pro	cca Pro 475	agc Ser	cac His	cct Pro	ccc Pro	agc Ser 480	ttc Phe	aac Asn	GJ Å GGG	gaa Glu	ggg Gly 485	ctg Leu	gag Glu	ggc .Gly	2693
cct Pro	cgg Arg 490	gtg Val	agc Ser	atg Met	ctg Leu	cca Pro 495	tcc Ser	ggc Gly	gtg Val	Gly ggg	cca Pro 500	gag Glu	tac Tyr	gca Ala	gag Glu	2741
cgc Arg 505	ccc Pro	gag Glu	gtg Val	gct Ala	cgc Arg 510	cgg	gac Asp	agc Ser	gcc Ala	ccc Pro 515	acc Thr	gag Gl <sub>u</sub>	agc Ser	cgg Arg	ctg Leu 520	2789
gcc Ala	aag Lys	agc Ser	gat Asp	gtg Val 525	ccc Pro	atc Ile	cag Gln	ctg Leu	ctc Leu 530	agc Ser	gcc Ala	acc Thr	aac Asn	cag Gln 535	ttc Phe	2837
cag Gln	agg Arg	cag Gln	gcg Ala 540	Ala	gtg Val	cag Gln	cag Gln	cag Gln 545	atc Ile	ccc Pro	acc Thr	aag Lys	ctg Leu 550	gcg Ala	gcc Ala	2885
tcc Ser	acc Thr	aag Lys 555	Gly	ggc	aag Lys	gac Asp	aag Lys 560	Gly	ggc Gly	aag Lys	agc Ser	agg Arg 565	ggc Gly	tct Ser	cag Gln	2933
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aac Asr 585	Lys	cto Leu	atg Met	ggg Gly	aaa Lys 590	Asp	gag Glu	agc Ser	acc Thr	Ser 595	Arg	aac Asn	cgc Arg	cgc	tcg Ser 600	3029
cto Lev	g ago 1 Ser	cct Pro	ato Ile	ctg Lev 605	Pro	ggc Gly	aga Arg	cac His	ser 610	Pro	gcg Ala	r ccc	cca Pro	eca Pro 615	gac Asp	3077
ect Pro	ggc Gly	tto Phe	e ccc Pro 620	Ala	ccg Pro	ago Ser	Pro	ccg Pro 625	Pro	gct Ala	gac Asp	ago Ser	Pro 630	Ser	gag Glu	3125
gg(	tto Phe	tct Ser 635	Leu	aag Lys	gco Ala	: ggg	ggc Gly 640	Thr	gco Ala	cto Lev	ctg Lev	Pro 645	Gly	e ccc	c cca o Pro	3173
		) Sei					Thi					Lys			gcc Ala	3221
	r Lys			gto Val		Phe			ı aa <u>q</u>	igg (	ecgts	gacto	a ag	gaaa	agttt	3273

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agt Ser 265	gac Asp	agt Ser	gac Asp	att Ile	cct Pro 270	gly ggg	agc Ser	tct Ser	gag Glu	gaa Glu 275	tcg Ser	ccg Pro	cag Gln	gtg Val	gtg Val 280	2069
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cta Lev	a cgc 1 Arg 410	ς Glι	g cgg L Arg	ctg Leu	gag Glu	cag Gln 415	Glu	cgg Arg	gcc Ala	gag Glu	ctg Lev 420	ı Glu	cgc Arg	cag Glr	cgc Arg	2501

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Ala Glu Met Gly Gly Leu Glu Asp Leu Pro Gln Pro Arg Gly Leu Phe 155 160 165

W	O 01/5	55437									•			1	PCT/US	801/02623
Leu 3620	Phe	Ala	Ala		Ser 3625	Glu	Glu	Gln		Glu 3630	Ser	Trp	Trp	_	Ala 635	
_		_	Thr	_	_	cag Gln	_	Leu	_				Lys	-		11181

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tgt cta ctc agg tct gat ccc tga ggtgaacccc agtgcaacac caaacttcag 11283 Cys Leu Leu Arg Ser Asp Pro \* 3670 3675

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			gag gag gct tgg Glu Glu Ala Trp	
Arg Trp Gln			ctg cag aag ctt Leu Gln Lys Leu 3425	
			tgc tgg gag gga Cys Trp Glu Gly 3440	
		s Ser Val Ser	gat gtg gag ttg Asp Val Glu Leu 3455	
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ggc agg aaa Gly Arg Lys 1 3605	cac aca ttc to His Thr Phe Se 361	er Leu Arg Leu	acc agt ggg gca Thr Ser Gly Ala 3615	gag atc 11085 Glu Ile
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His Gln Leu Glu Arg Glu Thr Leu Leu Leu Asp Ala Trp Leu Thr Thr 3110 3115 3120	
aag geg gee ace gee gag tee eag gae tae ggg eag gae etg gag ggt Lys Ala Ala Thr Ala Glu Ser Gln Asp Tyr Gly Gln Asp Leu Glu Gly 3125 3130 3135	9645
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gca gct ccg ggg ggc ctg gcc aag gtg cag gag gcc tgg gcc acc ctg Ala Ala Pro Gly Gly Leu Ala Lys Val Gln Glu Ala Trp Ala Thr Leu 3285 3290 3295	10125
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gcc cgg cgg ctg ctt cag agg ttc aag agc ctg agg gag ccc ctg cag Ala Arg Arg Leu Leu Gln Arg Phe Lys Ser Leu Arg Glu Pro Leu Gln 2870 2875 2880	8877
gag cgc agg acg gcc ctg gag gcc cgg agc ctc ctc ttg aag ttc ttc Glu Arg Arg Thr Ala Leu Glu Ala Arg Ser Leu Leu Lys Phe Phe 2885 2890 2895	8925
agg gac gcc gac gag gaa atg gcc tgg gtg cag gag aag ctg cct ctg Arg Asp Ala Asp Glu Glu Met Ala Trp Val Gln Glu Lys Leu Pro Leu 2900 2905 2910 2915	8973
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Gln Ala					Thr Ala	cgc ggc c Arg Gly L 2640		8157
		Pro Glu				agg tgc c Arg Cys G		8205
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	Leu Glu					ctg cag g Leu Gln A 26		8301
			Leu Arg			gtg gcc t Val Ala L 2705		8349
Glu Gly		-		-	Ala Gln	tta cag a Leu Gln L 2720		8397
		Ala Glu				caa cag c Gln Gln G		8445
ctg cag Leu Gln 2740	cgg gag Arg Glu	gga cag Gly Gln 2745	agg ctg Arg Leu	Leu Gln	ggg ggc Gly Gly 2750	cac cca g His Pro A	cc tcg la Ser 2755	8493
	Ile Gln					ctc tgg g Leu Trp G 27		8541
			Lys Lys			cag aag g Gln Lys A 2785		8589
Glu Ala					Glu Leu	gag aac t Glu Asn T 2800		8637
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cct ggg Pro Gly 2820	gtg ggc Val Gly	gag ctc Glu Leu 2825	ctg ggc Leu Gly	Thr Gln	agg gag Arg Glu 830	ctg gag g Leu Glu A	ca gca la Ala 2835	8733
	Lys Lys					ggc cag g Gly Gln A 28	la Glu	8781
gcc ttt	gtg agg	gaa ggc	cac tgc	ctt gcc	cga gat	gtg gaa g	ag cag	8829

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Glu Leu Asp	aat gtc acc aag Asn Val Thr Lys 2375	agg att cag g Arg Ile Gln G 2380	gag aag gaa gcc ct Slu Lys Glu Ala Le 2385	g atc 7389 u Ile
cag gcc ctg Gln Ala Leu 2390	Asp Cys Gly Lys	gat ctg gag a Asp Leu Glu S 2395	agc gtg cag agg ct Ger Val Gln Arg Le 2400	g ctg 7437 u Leu
Arg Lys His 2405	Glu Glu Leu Glu 2410	Arg Glu Val F	cac ccc atc cag gc lis Pro Ile Gln Al: 2415	a Gln
Val Glu Ser 2420	Leu Glu Arg Glu 2425	Val Gly Arg I 24	etc tgc caa aga ag Leu Cys Gln Arg Se: 130	r Pro 2435
gag gca gcc Glu Ala Ala	cac ggc ctc agg His Gly Leu Arg 2440	cac agg cag o His Arg Gln G 2445	ag gag gtg gct gag In Glu Val Ala Glu 2450	ı Ser
Trp Trp Gln	ctc cgg agc agg Leu Arg Ser Arg 2455	gcc cag aag c Ala Gln Lys A 2460	ngg agg gag gcg ctg arg Arg Glu Ala Lei 2465	g gat 7629 1 Asp
gcc ttg cac Ala Leu His 2470	Gln Ala Gln Lys	ctc cag gca a Leu Gln Ala M 2475	itg ctg cag gaa tto Met Leu Gln Glu Leo 2480	g ctg 7677 1 Leu
Val Ser Ala 2485	Gln Arg Leu Arg 2490	Ala Gln Met A	gac acg agc ccc`gct Asp Thr Ser Pro Ala 2495	a Pro
cgc agc cct Arg Ser Pro 2500	gtg gaa gcc cgg Val Glu Ala Arg 2505	Arg Met Leu G	gaa gag cat cag gag lu Glu His Gln Glu ilo	g tgc 7773 1 Cys 2515
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Thr Gly Gln	Gln Leu Leu Thr 2535	Ala Gly His F 2540	cc ttc agc tcc gad Pro Phe Ser Ser Asp 2545	) Ile
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gaa gac tcc	cta gcc agt gag	ggt cta tgg g	ac ccc ttg gcc ccc	atg 8061

Val Glu Gln Leu Ile Arg Lys His Glu Val Phe Leu Lys Val Leu Thr 2085 2090 gcc cag gac aag aag gag gca gcc ctg cgt gag cgg ctg aag acg ctc 6573 Ala Gln Asp Lys Lys Glu Ala Ala Leu Arg Glu Arg Leu Lys Thr Leu 2100 2105 2110 egg ege eee egg gtg egg gae egg ett eee ate etg etg eag ege egg 6621 Arg Arg Pro Arg Val Arg Asp Arg Leu Pro Ile Leu Leu Gln Arg Arg 2125 atg aga gtg aag gag ctg gcg gag agc cgg gga cac gcc ctg cat gcc 6669 Met Arg Val Lys Glu Leu Ala Glu Ser Arg Gly His Ala Leu His Ala 2140 tee etg etg atg gee age tte ace eag gee gea ace eag get gag gae 6717 Ser Leu Leu Met Ala Ser Phe Thr Gln Ala Ala Thr Gln Ala Glu Asp 2150 2155 tgg atc cag gcg tgg gcc cag cag ctg aag gag ccg gtc cct cct ggg 6765 Trp Ile Gln Ala Trp Ala Gln Gln Leu Lys Glu Pro Val Pro Pro Gly gac ctg aga gat aag ctg aag ccc ctg ctg aaa cac cag gcc ttt gag 6813 Asp Leu Arg Asp Lys Leu Lys Pro Leu Leu Lys His Gln Ala Phe Glu 2180 2185 gct gaa gtc cag gcc cat gag gag gtc atg acc tct gtt gcc aag aag 6861 Ala Glu Val Gln Ala His Glu Glu Val Met Thr Ser Val Ala Lys Lys 2200 2205 gga gag gct ctc ctg gca cag agt cac cct cga gcc gga gag gtc tcc 6909 Gly Glu Ala Leu Leu Ala Gln Ser His Pro Arg Ala Gly Glu Val Ser 2220 cag cgg ctg cag ggc ctg cgg aag cac tgg gag gac ctg agg cag gca 6957 Gln Arg Leu Gln Gly Leu Arg Lys His Trp Glu Asp Leu Arg Gln Ala 2235 atg gcc ctc agg ggc cag gag ctg gag gac agg cgg aac ttc ctg gag 7005 Met Ala Leu Arg Gly Gln Glu Leu Glu Asp Arg Arg Asn Phe Leu Glu 2250 ttc ctg cag aga gtg gac ctt gca gag gcc tgg atc cag gag aag gag 7053 Phe Leu Gln Arg Val Asp Leu Ala Glu Ala Trp Ile Gln Glu Lys Glu 2260 2270 2275 gtg aag atg aat gtt ggt gac ctg ggc cag gac ctg gag cac tgc ctg 7101 Val Lys Met Asn Val Gly Asp Leu Gly Gln Asp Leu Glu His Cys Leu 2280 2285 cag etc ega egg egg etc ege gag tte ega gga aac teg gee ggg gae 7149 Gln Leu Arg Arg Arg Leu Arg Glu Phe Arg Gly Asn Ser Ala Gly Asp 2300 aca gtg ggt gat gcc tgc atc agg agc atc agt gac ttg tca ctg cag 7197 Thr Val Gly Asp Ala Cys Ile Arg Ser Ile Ser Asp Leu Ser Leu Gln 2315 ctc aag aac cgg gac cct gag gaa gtc aag atc atc tgc cag cgg cga 7245 Leu Lys Asn Arg Asp Pro Glu Glu Val Lys Ile Ile Cys Gln Arg Arg 2330 age cag etc aac agg tgg geg agt tte cat gge aac ttg etc egg 7293

Ala Arq Gly His Ala Leu Arq Asp Thr Glu Thr Thr Leu Arq Val His 1835 aga gat etc ttg gaa gte etc ace eag gte eag gag aaa gee acg age 5805 Arg Asp Leu Leu Glu Val Leu Thr Gln Val Gln Glu Lys Ala Thr Ser 1850 1855 ctc ccc aac aat gtg gca cgg gac ctg tgt ggg ctg gag gcg cag ctg 5853 Leu Pro Asn Asn Val Ala Arg Asp Leu Cys Gly Leu Glu Ala Gln Leu 1865 aga agc cac cag ggg ctg gag cga gaa ctc gtg ggc acc gag cgg cag 5901 Arg Ser His Gln Gly Leu Glu Arg Glu Leu Val Gly Thr Glu Arg Gln 1880 ctg cag gaa ctg ctg gag act gca ggc agg gtg cag aag ctg tgt ccg 5949 Leu Gln Glu Leu Leu Glu Thr Ala Gly Arg Val Gln Lys Leu Cys Pro 1895 1900 ggg cct cag gcc cat gcg gtg cag cag agg cag caa gct gtg acg cag 5997 Gly Pro Gln Ala His Ala Val Gln Gln Arg Gln Gln Ala Val Thr Gln 1915 geg tgg gea gtg ctg cag cga cgc atg gag cag cgc agg gcc cag ctg 6045 Ala Trp Ala Val Leu Gln Arg Arg Met Glu Gln Arg Arg Ala Gln Leu 1930 gag egg gea ege ete etg gee ege tte ege aeg geg gtg egt gae tat 6093 Glu Arg Ala Arg Leu Leu Ala Arg Phe Arg Thr Ala Val Arg Asp Tyr 1945 1950 gcc tcc tgg gca gcc cgc gtg cgc cag gac ctg cag gtg gag gag agt 6141 Ala Ser Trp Ala Ala Arg Val Arg Gln Asp Leu Gln Val Glu Glu Ser 1960 1965 tcg caa gag cct agc agt ggc ccg ctg aag ctc agt gcc cac cag tgg 6189 Ser Gln Glu Pro Ser Ser Gly Pro Leu Lys Leu Ser Ala His Gln Trp 1975 1980 ctc cgg gcg gag ctg gag gcc cgg gag aag ctg tgg cag cag gcc acc 6237 Leu Arg Ala Glu Leu Glu Ala Arg Glu Lys Leu Trp Gln Gln Ala Thr 1990 1995 cag ctg ggg cag cag gca ctt ctt gct gca ggg aca ccc acc aag gaq 6285 Gln Leu Gly Gln Gln Ala Leu Leu Ala Ala Gly Thr Pro Thr Lys Glu gtc cag gaa gag ctt cga gcc ctg cag gac cag cgg gac cag gtg tat 6333 Val Gln Glu Glu Leu Arg Ala Leu Gln Asp Gln Arg Asp Gln Val Tyr 2025 2030 cag acc tgg gca cgg aag caa gag agg ctg cag gcc gag cag cag gag 6381 Gln Thr Trp Ala Arg Lys Gln Glu Arg Leu Gln Ala Glu Gln Glu Gln Glu 2045 cag etc ttc etc aga gag tgc ggc egc etg gag gag atc etc geg gec 6429 Gln Leu Phe Leu Arg Glu Cys Gly Arg Leu Glu Glu Ile Leu Ala Ala 2055 cag gag gtc tcc ctg aaa acc agt gcc ttg ggg agc tcg gtg gaa gag 6477 Gln Glu Val Ser Leu Lys Thr Ser Ala Leu Gly Ser Ser Val Glu Glu 2070 2075 2080 gta gag cag ttg att cgc aag cac gag gtc ttc ctg aag gtt ctg act 6525

His G		Gln ' 1575	Val Gln	Arg		Leu 1580	Ser	Ser	Gly		Ser 1585	Leu	Ala	
gcc t Ala S	ca ggg er Gly 1590	His	ccc caa Pro Gln	Ala	caa Gln 1595	cac His	atc Ile	gtg Val	Glu	cag Gln 1600	tgc Cys	cag Gln	gag Glu	5037
Leu G			tgg gca Trp Ala					Āla						5085
			cag gct Gln Ala 1625	Val			Gln					Asp		5133
tca g Ser G	ag ctg lu Leu	Glu (	ggc tgg Gly Trp 640	gtg Val	gag Glu	Glu	aag Lys 1645	cgg Arg	ccg Pro	ctg Leu	Val	agc Ser 1650	agt Ser	5181
cgg g Arg A	sp Tyr	ggc a Gly a 1655	aga gac Arg Asp	gag Glu	Ala	gcc Ala 1660	acc Thr	ctc Leu	agg Arg	Leu	att Ile .665	aac Asn	aag Lys	5229
cac c His G	ag gct ln Ala 1670	Leu (	cag gag Gln Glu	Glu	cta Leu 1675	gcc Ala	att Ile	tac Tyr	Trp	agc Ser 1680	tcc Ser	atg Met	gag Glu	527 <b>7</b>
	eu Asp		acg gcc Thr Ala					Gly						5325
cag c Gln G 1700	ag cgt ln Arg	gtg g Val V	gtg cag Val Gln 1705	gag Glu	agg Arg	ctc Leu	Arg	gag Glu 1710	cag Gln	ctg Leu	cgg Arg	Ala	ctg Leu 1715	5373
cag g Gln G	ag ttg lu Leu	Ala A	gcc aca Ala Thr 720	cgg Arg	gac Asp	Arg	gaa Glu 1725	ctg Leu	gag Glu	gly aaa	Thr	ctg Leu .730	agg Arg	5421
ctg c Leu H	is Glu	ttc o Phe I 1735	etg agg Leu Arg	gag Glu	Ala	gag Glu 1740	gac Asp	ctg Leu	cag Gln	Gly	tgg Trp 745	ctg Leu	gca Ala	5469
agc ca Ser G	ag aag ln Lys 1750	cag g Gln A	gca gcc Ala Ala	Lys	gga Gly L755	gly aaa	gag Glu	agc Ser	Leu	gga Gly .760	gag Glu	gac Asp	ccc Pro	5517
gag ca Glu H: 170	is Ala	ctg o	eac ctc His Leu	tgc Cys 1770	acc Thr	aag Lys	ttt Phe	Ala	aag Lys 775	ttt Phe	cag Gln	cac His	caa Gln	5565
gtg ga Val G 1780	ag atg lu Met	ggc a	igc cag Ser Gln 1785	cgg Arg	gtg Val	gcc Ala	Ala	tgc Cys 790	cgg Arg	ctg Leu	ctg Leu	Ala	gag Glu 795	5613
agc ct Ser Le	tg cta eu Leu	Glu A	gt ggg rg Gly	cac His	agt Ser	Ala	ggc Gly 805	ccc Pro	atg Met	gtc Val	Arg	cag Gln 810	agg Arg	5661
cag ca Gln Gl	ln Asp	ctg c Leu G 1815	ag acc	gcc Ala	Trp	tcg Ser 820	gag Glu	ctg Leu	tgg Trp	Glu :	ctg Leu 825	acc Thr	cag Gln	5709
gcc cg	ga ggc	cac g	cg ctc	cga	gac	acc	gag	acc	acc	ctc	aga	gtt	cac	5757

Leu Gln Glu Trp Lys Gln Asp Val Ala Glu Leu Met Gln Trp Met Glu gag aag ggg ctg atg gct gcg cat gag ccc tcc gga gcg cgc aga aac 4269 Glu Lys Gly Leu Met Ala Ala His Glu Pro Ser Gly Ala Arg Arg Asn 1340 1335 atc ctq caq aca ctc aag cgg cac gaa gca gct gag agc gag cta ctc 4317 Ile Leu Gln Thr Leu Lys Arg His Glu Ala Ala Glu Ser Glu Leu Leu 1355 1350 gec acc ege aga cae gtg gag gec etg cag cag gtt ggg aga gag etg 4365 Ala Thr Arg Arg His Val Glu Ala Leu Gln Gln Val Gly Arg Glu Leu 1365 1370 ttg agt agg agg ccc tgt ggc cag gag gac ata cag acc agg ctt caa 4413 Leu Ser Arg Arg Pro Cys Gly Gln Glu Asp Ile Gln Thr Arg Leu Gln 1380 1385 1390 ggc ctg aga agc aag tgg gaa gct ttg aac cgc aag atg act gag cgt 4461 Gly Leu Arg Ser Lys Trp Glu Ala Leu Asn Arg Lys Met Thr Glu Arg 1405 1400 ggg gac gag ctc cag cag gct gga cag cag gag caa ctc ctg agg cag 4509 Gly Asp Glu Leu Gln Gln Ala Gly Gln Glu Gln Leu Leu Arg Gln 1420 ctg cag gat gca aag gag cag ctg gag cag ctc gaa ggg gcc cta cag 4557 Leu Gln Asp Ala Lys Glu Gln Leu Glu Gln Leu Glu Gly Ala Leu Gln 1435 1440 age teg gaa aca ggg cag gae etg ege tee age cag agg etg cag aaa 4605 Ser Ser Glu Thr Gly Gln Asp Leu Arg Ser Ser Gln Arg Leu Gln Lys egg cae caa cag etg gag agt gag age egg ace etg get gee aag atg 4653 Arg His Gln Gln Leu Glu Ser Glu Ser Arg Thr Leu Ala Ala Lys Met 1465 1460 .1470 get ged etc ged ted atg ged dat ggd atg ged ged ted deg ged atc 4701 Ala Ala Leu Ala Ser Met Ala His Gly Met Ala Ala Ser Pro Ala Ile 1480 1485 ctg gaa gag acc cag aag cac ctc cgg agg ctg gag ctt ctg cag ggg 4749 Leu Glu Glu Thr Gln Lys His Leu Arg Arg Leu Glu Leu Leu Gln Gly 1500 cat ctg gcc atc cgg ggc ctg cag ctg cag gcc tca gtg gag ctg cac 4797 His Leu Ala Ile Arg Gly Leu Gln Leu Gln Ala Ser Val Glu Leu His 1515 cag tto tgc cac ctg ago aac atg gag ctc tot tgg gta gcc gag cac 4845 Gln Phe Cys His Leu Ser Asn Met Glu Leu Ser Trp Val Ala Glu His 1530 1535 atg ccc cat ggc agc ccc acc agc tat acc gag tgc ttg aat ggt qcc 4893 Met Pro His Gly Ser Pro Thr Ser Tyr Thr Glu Cys Leu Asn Gly Ala 1540 1555 cag ago ott cac ogo aag cac aag gag oto cag gtg gag gta aaa got 4941 Gln Ser Leu His Arg Lys His Lys Glu Leu Gln Val Glu Val Lys Ala 1560 1565 1570 cac cag ggg cag gtg caa cgg gtg ctg agt tet ggg egg agc etg gea

Val Lys 1060	Val Glu	Glu Pro 1065	Gly Tyr	Ala Gl	u Ser Gl	n Pro Leu	Gln Gly 1075	
cag gtg Gln Val	gag aca Glu Thi	a ctg cag r Leu Gln 1080	ggg ctg Gly Leu	ctg aa Leu Ly 108	s Gln Va	a cag gaa l Gln Glu	caa gtg Gln Val 1090	3501
gcc caa Ala Gln	cgg gcc Arg Ala 1099	a Arg Arg	Gln Ala	gag ac Glu Th 1100	t cag gc r Gln Al	c cgg cag a Arg Gln 1105	agc ttc Ser Phe	3549
Leu Gln		_	_			g agt gtc u Ser Val 1120		3597
		r Lys Glu				c tcg gct a Ser Ala 5		3645
						c cac ctg e His Leu		3693
					r Gln Pr	c atg gca o Met Ala		3741
		Ser Gln	Glu Val			g agg gtc u Arg Val 1185		3789
Gln Gln				-		g agg cag n Arg Gln 1200		3837
_		Leu Glu		-		a gaa gtg g Glu Val 5		3885
						g cac ctg u His Leu		3933
					r Leu Lei	g cag cag ı Gln Gln		3981
		Leu Leu	Ser Thr			g gca gag g Ala Glu 1265		4029
Arg Ala					_	c cca gct s Pro Ala 1280	_	4077
		ı Gln Leu				g tgg acc n Trp Thr		4125
						g gct tcc ı Ala Ser		4173
ctc cag	gag tgg	aag cag	gat gtg	gca ga	g ctg ato	g cag tgg	atg gaa	4221

***	<b>J</b> 01/3	3437												•	C1/0	301,02020
Leu	Glu 805	Glu	Gln	Gly	Arg	Ala 810	Ala	Ser	Ala	Arg	Ala 815	Ser	Leu	Phe	Thr	
			gcc Ala											Pro		2733
			gag Glu													2781
atg Met	gcc Ala	ctc Leu	cca Pro 855	gct Ala	gag Glu	cct Pro	gac Asp	cct Pro 860	gac Asp	ttt Phe	gat Asp	ccc Pro	aac Asn 865	act Thr	ata Ile	2829
			cag Gln													2877
			ctc Leu													2925
			agt Ser													2973
aca Thr	gtg Val	ctg Leu	ctc Leu	caa Gln 920	agg Arg	gtg Val	cag Gln	ccc Pro	cag Gln 925	gct Ala	gac Asp	acc Thr	ctg Leu	gag Glu 930	gtc Val	3021
			aaa Lys 935													3069
			gct Ala													3117
			aac Asn						-	_	-		_	_	_	3165
_	Arg		gj aaa													3213
_	_		agt Ser		-		_	Ser		_	_		Cys			3261
		Val	cag Gln 1015	Leu			Val					Glu				3309
	Gly		tca Ser			Thr					Gln					3357
Lys	_	Leu	gtg Val	_	Glu			-		Phe			_		-	3405
gta	aag	gtc	gag	gag	cca	ggc	tac	gca	gag	agc	cag	cct	ctg	caa	gga	3453

WC	01/5	5437												r	C1/0	301/02023
Gln	Leu	Glu 550	Glu	Leu	Gln	Glu	Pro 555	Ala	Arg	Ser	Thr	Ala 560	Сув	Gly	Gln	
cag Gln	ctg Leu 565	gca Ala	gaa Glu	gtg Val	gtg Val	gag Glu 570	ctg Leu	ctg Leu	cag Gln	agg Arg	cat His 575	gac Asp	ctg Leu	ctg Leu	gag Glu	1965
gct Ala 580	caa Gln	gtc Val	tcg Ser	gcc Ala	cac His 585	gga Gly	gcc Ala	cat His	gtg Val	agc Ser 590	cat His	ctt Leu	gct Ala	cag Gln	cag Gln 595	2013
aca Thr	gca Ala	gag Glu	ctg Leu	gac Asp 600	tcc Ser	tcc Ser	ctg Leu	ggc Gly	acc Thr 605	agt Ser	gtg Val	gag Glu	gtg Val	ctg Leu 610	cag Gln	2061
gcc Ala	aag Lys	gcc Ala	agg Arg 615	aca Thr	ctg Leu	gcc Ala	cag Gln	ctc Leu 620	caa Gln	cag Gln	agc Ser	ctg Leu	gtg Val 625	gct Ala	ctt Leu	2109
gtc Val	agg Arg	gcc Ala 630	cgg Arg	cgg Arg	gcc Ala	ctg Leu	ctg Leu 635	gag Glu	cag Gln	acc Thr	ctg Leu	cag Gln 640	cgg Arg	gca Ala	gag Glu	2157
ttc Phe	ctg Leu 645	cgc Arg	aac Asn	tgt Cys	gag Glu	gag Glu 650	gag Glu	gaa Glu	gcc Ala	tgg Trp	ctg Leu 655	aag Lys	gag Glu	tgc Cys	gga Gly	2205
cag Gln 660	cgg Arg	gtg Val	ggg	aat Asn	gcg Ala 665	gcc Ala	ctg Leu	ggc Gly	cgg Arg	gat Asp 670	ctc Leu	agc Ser	cag Gln	atc Ile	gca Ala 675	2253
ggc Gly	gcc Ala	ctg Leu	cag Gln	aaa Lys 680	cac His	aag Lys	gcc Ala	ctg Leu	gaa Glu 685	gct Ala	gag Glu	gtc Val	cac His	cgc Arg 690	cac His	2301
					gat Asp											2349
cgc Arg	agg Arg	ccc Pro 710	cca Pro	acg Thr	cag Gln	ccg Pro	gat Asp 715	ccc Pro	Gly aaa	gaa Glu	cgg Arg	gca Ala 720	gag Glu	gcc Ala	gtt Val	2397
cag Gln	gga Gly 725	Gly	Trp	Gln	ctg Leu	Leu	Gln	Thr	Arg	Val	Val	Gly	cgg Arg	ggc	gca Ala	2445
cgg Arg 740	Leu	cag Gln	aca Thr	gcc Ala	ctg Leu 745	ctg Leu	gtc Val	ctg Leu	cag Gln	tac Tyr 750	ttc Phe	gcg Ala	gac Asp	gcg Ala	gcg Ala 755	2493
					ctg Leu											2541
					cag Gln											2589
gtg Val	cgg Arg	ctg Leu 790	gag Glu	cgc Arg	gtc Val	ctg Leu	cgc Arg 795	gcc Ala	ttc Phe	gcg Ala	gcc Ala	gag Glu 800	ctg Leu	cgg Arg	cgg Arg	2637
ctg	gag	gag	cag	<b>3</b> 99	cgg	gcg	gcc	tcg	gcc	cgg	gcg	tcg	tta	ttc	acg	2685

WC	01/5	3437													CI/US	01/02023
Arg	Arg	Leu	Thr 295	Lys	Ile	Leu	Leu	Gln 300	Leu	Gln	Glu	Thr	Glu 305	Leu	Leu	
				gag Glu												1197
				cag Gln												1245
-	_		_	cta Leu	_	_	-					-		_		1293
				cta Leu 360												1341
		_		gca Ala			-	_		_				-		1389
			_	ggc Gly		-		_			-		-			1437
		_		gct Ala	-		_	_	_	_	_	-			-	1485
cag Gln 420	ctg Leu	cag Gln	cgg Arg	cta Leu	gaa Glu 425	acc Thr	ctg Leu	gcc Ala	cgg Arg	cgc Arg 430	ttc Phe	cag Gln	cgc Arg	aag Lys	gca Ala 435	1533
				agt Ser 440									Leu			1581
gcc Ala	aga Arg	gcc Ala	ccg Pro 455	cca Pro	gcc Ala	agc Ser	ctg Leu	gcc Ala 460	aca Thr	gtg Val	gag Glu	gca Ala	gcc Ala 465	gtc Val	cag Gln	1629
			Met	ctg Leu		Ala	Gly	Ile	Leu	Pro		Glu	Gly			1677
				gag Glu												1725
agc Ser 500	tgg Trp	gca Ala	gat Asp	gtg Val	gcc Ala 505	cgc Arg	agg Arg	cag Gln	gag Glu	gaa Glu 510	gtt Val	acc Thr	gtg Val	cgc Arg	tgg Trp 515	1773
cag Gln	agg Arg	ctc Leu	ctt Leu	cag Gln 520	cat His	cta Leu	cag Gln	gga Gly	cag Gln 525	agg Arg	aag Lys	cag Gln	gtg Val	gca Ala 530	gac Asp	1821
atg Met	cag Gln	gct Ala	gtg Val 535	ctg Leu	agc Ser	ctg Leu	ctg Leu	cag Gln 540	gag Glu	gtg Val	gag Glu	gct Ala	gcc Ala 545	tcc Ser	cac His	1869
cag	ctg	gag	gag	ctg	cag	gag	ccg	gcc	agg	tcc	acc	gcc	tgt	aaa	cag	1917

Met	Asp	Ser	Gln	Tyr 40	Glu	Thr	Gly	His	Ile 45	Arg	Lys	Leu	Gln	Ala 50	Arg	
								ttc Phe 60								429
	_	_		_				aag Lys				-			_	477
								cgg Arg								525
								ggc Gly								573
		_	_	_	_	_	_	ttc Phe			_				_	621
								gtg Val 140	_		_					669
_					_			ctg Leu	_		_					717
								gcc Ala		-	-	-	_			765
								cag Gln								813
								cga Arg								861
		-				-		agg Arg 220		_	_	_	_			909
					-		-	cac His			-		-		-	957
								gct Ala								1005
gtg Val 260	gca Ala	gcc Ala	gca Ala	cag Gln	cca Pro 265	gat Asp	gag Glu	cgc Arg	tct Ser	atc Ile 270	atg Met	acc Thr	tac Tyr	gtc Val	tcc Ser 275	. 1053
								ctg Leu								1101
agg	aga	ctc	act	aag	atc	ctg	ctt	cag	ctc	cag	gag	aca	gag	ctg	ctg	1149

WO 01/55437 PCT/US01/02623 tot cag ggt aac ctg act gag too tgg gca gat gat aac coo cga cac 1073 Ser Gln Gly Asn Leu Thr Glu Ser Trp Ala Asp Asp Asn Pro Arg His 315 320 cat ggc ctg gct gcc cac tcc tca ggg gag gaa aga gag atc cag tat 1121 His Gly Leu Ala Ala His Ser Ser Gly Glu Glu Arg Glu Ile Gln Tyr gca ccc ctc agc ttt cat aag ggg gag cct cag gac cta tca ggt caa 1169 Ala Pro Leu Ser Phe His Lys Gly Glu Pro Gln Asp Leu Ser Gly Gln 355 gaa gcc acc aac aat gag tac tca gag atc aag atc ccc aag taa gaa 1217 Glu Ala Thr Asn Asn Glu Tyr Ser Glu Ile Lys Ile Pro Lys \* 365 370 aatgcagagg ctcgggcttg tttgagggtt cacgacccct ccagcaaagg agtctgaggc 1277 tgattccagt agaattagca gccctcaatg ctgtgcaaca agacatcaga acttattcct 1337 ettgtctaac tgaaaatgca tgcctgatga ccaaactetc cetttcccca tccaatcggt 1397 ccacactece egecetggee tetggtacee accattetee tetgtactte tetaaggatg 1457 actactttag attccgaata tagtgagatt gtaacgtgtt tgtctctctg tgcctqqctt 1517 atttcactca acataacatc ctctaagttc atctgtgttg tttccaatga cagagtaatg 1577 tactgaataa ttcaaaatag ctaaaagaga ggagtttaaa tgttgtcacc aaaaaaaaa 1637 aaaaa 1642

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<210> 218

20

381

atg gac tot cag tac gag acg ggc cac att cgc aag cta cag gcc cgg

WO 01/5543	7						PC7	T/US01/02623
gac tct gad Asp Ser Asp	cca gtt Pro Val	cat ggc His Gly	tac tgg Tyr Trp 65	Phe Ar	g gca g g Ala G	gg aat ly Asn 70	gat at Asp Il	a 305 e
agc tgg aag Ser Trp Lys	Ala Pro				o Ala T			
gag gaa act Glu Glu Thi 90								
aat tgc acc Asn Cys Thi 105		_	-		t Ser A			3
tac ttc tt! Tyr Phe Phe		Glu Lys				sn Tyr		
gac cag cto Asp Gln Lev			_		_	_	-	•
act gtc tto Thr Val Pho 159	: Gln Gly				r Ala Le			
tca tct ctt Ser Ser Let 170								
gtt gac ago Val Asp Sei 185	aat ccc Asn Pro	cct gcc Pro Ala 190	agg ctg Arg Leu	agc tgg Ser Trp 19	o Thr Ti	g agg	agt cto Ser Leo 20	ı
acc ctg tac Thr Leu Tyn	ccc tca Pro Ser 205	Gln Pro	tca aac Ser Asn	pro Let 210	g gta ct ı Val Le	u Glu	ctg caa Leu Gli 215	a 737
gtg cac cto Val His Lev	ggg gat Gly Asp 220	gaa ggg Glu Gly	gaa ttc Glu Phe 225	acc tgt Thr Cys	t cga go s Arg Al	t cag a Gln 230	aac tci Asn Sei	785
ctg ggt tcc Leu Gly Ser 235	Gln His					n Gln (		
aca ggc aaa Thr Gly Lys 250	atg agg Met Arg	cct gta Pro Val 255	tca gga Ser Gly	gtg ttg Val Leu	g ctg gg Leu Gl 260	gg gcg g .y Ala '	gtc ggg Val Gly	881
gga gct gga Gly Ala Gly 265	gcc aca Ala Thr	gcc ctg Ala Leu 270	gtc ttc Val Phe	ctc tcc Leu Ser 279	Phe Cy	rs Val	atc tto Ile Phe 280	<b>:</b>
att gta gtg Ile Val Val	agg tcc Arg Ser 285	tgc agg Cys Arg	aag aaa Lys Lys	tcg gca Ser Ala 290	a agg co a Arg Pr	o Ala A	gcg gad Ala Asp 295	977

gtg gga gac ata ggc atg aag gat gca aac acc atc agg ggc tca gcc Val Gly Asp Ile Gly Met Lys Asp Ala Asn Thr Ile Arg Gly Ser Ala

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														gaa Glu		1414
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	aag Lys		gaa	aatg	caga	aggci	tog (	ggcti	tgtti	tg ag	gggti	tcac	gac	ccct	ccag	1566
caa	agga	gtc	tgag	gctg	at t	ccag	taga	a tta	agca	dece	tca	atgci	tgt :	gcaa	caagac	1626
atc	agaa	ctt .	attc	ctct	tg t	ctaa	ctga	a aa	tgca	tgcc	tga	tgac	caa	actc	tccctt	1686
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		_				atc Ile									_	838
						ttc Phe										886
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tgg Trp 290	agg Arg	agt Ser	ctg Leu	acc Thr	ctg Leu 295	tac Tyr	ccc Pro	tca Ser	cag Gln	ccc Pro 300	tca Ser	aac Asn	cct Pro	ctg Leu	gta Val 305	1030
ctg Leu	gag Glu	ctg Leu	caa Gln	gtg Val 310	cac His	ctg Leu	Gly aaa	gat Asp	gaa Glu 315	gjå aaa	gaa Glu	ttc Phe	acc Thr	tgt Cys 320	cga Arg	1078
gct Ala	cag Gln	aac Asn	tct Ser 325	ctg Leu	ggt Gly	tcc Ser	cag Gln	cac His 330	gtt Val	tcc Ser	ctg Leu	aac Asn	ctc Leu 335	tcc Ser	ctg Leu	1126
caa Gln	cag Gln	gag Glu 340	tac Tyr	aca Thr	ggc Gly	aaa Lys	atg Met 345	agg Arg	cct Pro	gta Val	tca Ser	gga Gly 350	gtg Val	ttg Leu	ctg Leu	1174
gj aaa	gcg Ala 355	gtc Val	gly ggg	gga Gly	gct Ala	gga Gly 360	gcc Ala	aca Thr	gcc Ala	ctg Leu	gtc Val 365	ttc Phe	ctc Leu	tcc Ser	ttc Phe	1222
tgt Cys 370	gtc Val	atc Ile	ttc Phe	att Ile	gta Val 375	gtg Val	agg Arg	tcc Ser	tgc Cys	agg Arg 380	aag Lys	aaa Lys	tcg Ser	gca Ala	agg Arg 385	1270
cca Pro	gca Ala	gcg Ala	gac Asp	gtg Val 390	gga Gly	gac Asp	ata Ile	ggc Gly	atg Met 395	aag Lys	gat Asp	gca Ala	aac Asn	acc Thr 400	atc Ile	1318

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aaga	accc	tg a	ggaa	caga	c gt	tece	tcgc	ggc	cctg	gca	cctc	caac	cc c	agat	atg Met 1	118
ctg Leu	ctg Leu	ctg Leu	ctg Leu 5	ctg Leu	ctg Leu	ccc Pro	ctg Leu	ctc Leu 10	tgg Trp	Gly aaa	agg Arg	gag Glu	agg Arg 15	gtg Val	gaa Glu	166
gga Gly	cag Gln	aag Lys 20	agt Ser	aac Asn	cgg Arg	aag Lys	gat Asp 25	tac Tyr	tcg Ser	ctg Leu	acg Thr	atg Met 30	cag Gln	agt Ser	tcc Ser	214
gtg Val	acc Thr 35	gtg Val	caa Gln	gag Glu	ggc Gly	atg Met 40	tgt Cys	gtc Val	cat His	gtg Val	cgc Arg 45	tgc Cys	tcc Ser	ttc Phe	tcc Ser	262
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ctt Leu	Gly 999	gac Asp 100	cca Pro	cag Gln	acc Thr	aaa Lys	aat Asn 105	tgc Cys	acc Thr	ctg Leu	agc Ser	atc Ile 110	aga Arg	gat Asp	gcc Ala	454
aga Arg	atg Met 115	agt Ser	gat Asp	gcg Ala	GJ A aaa	aga Arg 120	Tyr	ttc Phe	ttt Phe	cgt Arg	atg Met 125	gag Glu	aaa Lys	gga Gly	aat Asn	502
ata Ile 130	aaa Lys	tgg Trp	aat Asn	tat Tyr	aaa Lys 135	tat Tyr	gac Asp	cag Gln	ctc Leu	tct Ser 140	gtg Val	aac Asn	gtg Val	aca Thr	gcc Ala 145	550

220 225 230

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	-		_		-					-		-		cat His		1253
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_		-	_			_		_		_			-	aca Thr	_	1541
		_	-		_		_					_	_	ttc Phe 360		1589
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gccg	geege	ccg c	cccc	acto	jc t <u>c</u>	tgto	cttt	. cca	gact	cca	ggg	etcco	cg g	gcto	ctctg	1997
gato	ccag	gga c	ctccg	gctt	t cg	ccga	gccg	r cag	cggg	atc	ccts	tgca	icc c	ggcg	rcagcc	2057

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tgctggcctg gcctggatct tccacc atg ttc ctg ttg ctg cct ttt gat agc 53 Met Phe Leu Leu Pro Phe Asp Ser · 1 5
ctg att gtc aac ctt ctg ggc atc tcc ctg act gtc ctc ttc acc ctc  Leu Ile Val Asn Leu Leu Gly Ile Ser Leu Thr Val Leu Phe Thr Leu  10 25 25
Ctt CtC gtt ttC atC ata gtg CCa gCC att ttt gga gtC tCC ttt ggt 62: Leu Leu Val Phe Ile Ile Val Pro Ala Ile Phe Gly Val Ser Phe Gly 30 35 40
atc cgc aaa ctc tac atg aaa agt ctg tta aaa atc ttt gcg tgg gct 67 Ile Arg Lys Leu Tyr Met Lys Ser Leu Leu Lys Ile Phe Ala Trp Ala 45 50 55
acc ttg aga atg gag cga gga gcc aag gag aag aac cac ca
aag ccc tac acc aac gga atc att gca aag gat ccc act tca cta gaa 77: Lys Pro Tyr Thr Asn Gly Ile Ile Ala Lys Asp Pro Thr Ser Leu Glu 75 80 85
gaa gag atc aaa gag att cgt cga agt ggt agt agt aag gct ctg gac 82: Glu Glu Ile Lys Glu Ile Arg Arg Ser Gly Ser Ser Lys Ala Leu Asp 90 95 100 105
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aat ggg agg ttt aag gag ttc atg agt aaa cat gtt cac tta atg tgt 1157 Asn Gly Arg Phe Lys Glu Phe Met Ser Lys His Val His Leu Met Cys 205 210 215
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	agg Arg															882
	gly															930
	ctg Leu															978
cgg Arg	Gly	ccc Pro 295	tgc Cys	cga Arg	gcc Ala	ttc Phe	atc Ile 300	cag Gln	ctc Leu	tgg Trp	gca Ala	ttt Phe 305	gat Asp	gct Ala	gtc Val	1026
aag Lys	310 GJA 333	aag Lys	tgc Cys	gtc Val	ctc Leu	ttc Phe 315	ccc Pro	tac Tyr	Gly aaa	ggc Gly	tgc Cys 320	cag Gln	ggc Gly	aac Asn	G1y aaa	1074
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ggt Gly	gat Asp	ggt Gly	gat Asp	gag Glu 345	gag Glu	ctg Leu	ctg Leu	cgc Arg	ttc Phe 350	tcc Ser	aac Asn	tgad	aac	tggc	cgg	1172
tcto	gcaag	jtc a	gagg	gatgo	jc ca	gtgt	ctgt	ccc	9999	rtcc	tgtg	gcag	ıgc a	gege	caago	1232
aaco	tggg	rtc c	aaat	aaaa	ıa ct	aaat	tgta	aac	tect	gaa	aaaa	aaaa	ı			1280

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ggg gcc ctg ctc ttg ctg ctg agc gcc tgc ctg gcg gtg agc gct ggc Gly Ala Leu Leu Leu Leu Ser Ala Cys Leu Ala Val Ser Ala Gly 5 10 15 20	162
cet gtg cea acg ceg cec gac aac atc caa gtg cag gaa aac ttc aat Pro Val Pro Thr Pro Pro Asp Asn Ile Gln Val Gln Glu Asn Phe Asn 25 30 35	210
atc tct cgg atc tat ggg aag tgg tac aac ctg gcc atc ggt tcc acc Ile Ser Arg Ile Tyr Gly Lys Trp Tyr Asn Leu Ala Ile Gly Ser Thr 40 45 50	258
tgc ccc tgg ctg aag aag atc atg gac agg atg aca gtg agc acg ctg Cys Pro Trp Leu Lys Lys Ile Met Asp Arg Met Thr Val Ser Thr Leu 55 60 65	306
gtg ctg gga gag ggc gct aca gag gcg gag atc agc atg acc agc act Val Leu Gly Glu Gly Ala Thr Glu Ala Glu Ile Ser Met Thr Ser Thr 70 . 75 80	354
cgt tgg cgg aaa ggt gtc tgt gag gag acg tct gga gct tat gag aaa Arg Trp Arg Lys Gly Val Cys Glu Glu Thr Ser Gly Ala Tyr Glu Lys 85 90 95 100	402
aca gat act gat ggg aag ttt ctc tat cac aaa tcc aaa tgg aac ata Thr Asp Thr Asp Gly Lys Phe Leu Tyr His Lys Ser Lys Trp Asn Ile 105 110 115	450
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ttc ctg acc aag aaa ttc agc cgc cat cat gga ccc acc att act gcc Phe Leu Thr Lys Lys Phe Ser Arg His His Gly Pro Thr Ile Thr Ala 135 140 145	546
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gaa gga tca ggg ggt ggg caa ctg gta act gaa gtc acc aag aaa gaa Glu Gly Ser Gly Gly Gln Leu Val Thr Glu Val Thr Lys Lys Glu 215 220 225	786

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cag Gln	cag Gln	tac Tyr 265	tac Tyr	gtg Val	aaa Lys	ctg Leu	aag Lys 270	gac Asp	aac Asn	gag Glu	aag Lys	aac Asn 275	cgg Arg	aag Lys	ctc Leu	1049
ttt Phe	gac Asp 280	ctt Leu	ctg Leu	gat Asp	gtc Val	ctt Leu 285	gag Glu	ttc Phe	aac Asn	cag Gln	gtg Val 290	gtg Val	atc Ile	ttt Phe	gtg Val	1097
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	_	_						_	_		_	_	_	atc Ile		1337
	-		_	_	_			_					_	cct Pro	-	1385
	ata Ile											tag *	aaga	actc	gee	1434
cat	tttg	gaa 1	tgtga	accgi	to to	gtcci	tcaç	g gag	gagga	acac	cag	ggtgg	agg 9	gtgaa	aggaga	1494
cac	tact	gec (	cca	cccc	g a	cagc	ccca	a cco	ccat	ggct	tcc	atcti	tt 9	gcato	caccac	1554
cac	tact	gaa (	cccc	catt	to to	gatti	gtc	a gaa	attt	ttt	ttaa	acaa	aac 1	taaaa	aatgaa	1614
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<220>

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	-														atcca	180	)
_																233	,
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gac a	aat g Asn (	gag Glu	ctc Leu 10	ttg ( Leu )	gac Asp	tat ( Tyr	gaa Glu	gat ( Asp . 15	gat Asp	gag Glu	gtg Val	gag Glu	aca Thr 20	gca Ala	gct Ala	281	L
Gly (	gga ( Gly	gat Asp 25	G1A aaa	gct ( Ala	gag Glu	gcc Ala	cct Pro 30	gcc Ala	aag Lys	aag Lys	gat Asp	gtc Val 35	aag Lys	ggc Gly	tcc Ser	329	9
tat (	gtc Val 40	tcc Ser	atc Ile	cac His	agc Ser	tct Ser 45	ggc Gly	ttt Phe	cgt Arg	gac Asp	ttc Phe 50	ctg Leu	ctc Leu	aag Lys	cca Pro	371	7
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cat His	atc Ile	gtc Val	gtg Val 170		act Thr	cca Pro	ggc	cgt Arg 175	Ile	cta Leu	gcc Ala	ctg Lev	gct Ala 180	Arg	aat Asn	76	51
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Phe Glu Val 1			ata gac atc tcc Ile Asp Ile Ser 420				
tac att gaa o Tyr Ile Glu o 425		aa gactcgccca t	tttggaatg tgaccgt	ctg 1534:			
teetteagga gaggacacea gggtgggggt gaaggagaca etaetgeeee cacceetgae 1594							
agccccacc co	catggette catet	tttgc atcaccacca	ctcctgaacc cccat	ttctg 1654			
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<221> CDS

<222> (216)..(1424)

<400> 213

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377							cgt Arg									
425	gaa Glu 70	tca Ser	ccg Pro	cat His	gag Glu	ttt Phe 65	ggc Gly	tgt Cys	gac Asp	gtc Val	att Ile 60	gcc Ala	cgg Arg	ctc Leu	ttg Leu	gag Glu 55
473							att Ile 80									
521							aca Thr									
569							gjå aaa									
617							cag Gln							His		
665	ggt Gly 150	ttt Phe	ttt Phe	gtt Val	gct Ala	gtt Val 145	aag Lys	gtc Val	aat Asn	ccc Pro	atg Met 140	tac Tyr	aaa Lys	tct Ser	Phe	ege Arg 135
713		_		_	_	-	gtg Val 160		-	_	Lys	_			_	
761				_	-		atc Ile	_				Gly		_		
809	_	_	-	_			cac His	Lys					Asn		_	_
857							cgt Arg		Asp					Met		
905			_		_	_	gtc Val	_	_	Glu				_	Arg	
953	cca Pro	_		_		Lys	cgc Arg 240	-	_		Arg				_	
1001	ttg Leu			_		_	Lys	-		_	_	Val				
1049	ctc - Leu								-	-						-

wo	01/5	5437												1	PCT/US0	1/02623
Leu 305	Phe	Gly	Gly	Thr	Ser 310	Pro	Ser	Pro	Glu	Glu 315	Gly	Leu	Gly	Asp	Glu 320	
														agc Ser 335		1186
														cta Leu		1234
_			-			_					_		-	atg Met		1282
		_			_	cgc Arg 375			_					tag *	gag	1330
gaag	jttt	ctg o	ccac	ctcc	cc to	cctga	agcct	gct	gtca	atct	tcad	etge	ecc 1	tgcc	catctg	1390
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cago	tget	ccc t	tggg	cctca	ag ct	tete	gecea	ggg	gccag	gccc	aggt	tcts	gct (	gggaa	agggaa	1630
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cttg	goota	atc o	ccct	ccct	c to	gette	gaged	ttg	gagco	cttg	acto	ggag	get q	gaaag	gagtt	1750
gcag	ctgt	tg g	gcate	gagad	cc to	ectto	ctccc	cgt	ctto	<b>3</b> 333	aggt	gggg	gac (	cagca	igataa	1810
atco	caco	cct t	tccti	ttgai	nt gt	cgct	gtac	tct	gaag	gttc	agct	agct	ca	gattt	tataa	1870
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Phe	Asn 50	Ala	Val	Ser	Leu	Arg 55	Trp	Thr	Lys	Leu	Pro 60	Pro	Val	Lys	Ser	
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tca Ser	acc Thr	gtc Val	ctc Leu	atc Ile 85	gac Asp	gac Asp	aca Thr	gtc Val	ctc Leu 90	ctt Leu	tgg Trp •	ggc Gly	gjå aaa	cgg Arg 95	aat Asn	466
gac Asp	acc Thr	gaa Glu	ggg Gly ggg	gcc Ala	tgc Cys	aat Asn	gtg Val	ctc Leu 105	tat Tyr	gcc Ala	ttt Phe	gac Asp	gtc Val 110	aat Asn	acg Thr	514
cac His	aag Lys	tgg Trp 115	ttc Phe	aca Thr	ccc Pro	cga Arg	gtg Val 120	tca Ser	Gly 999	aca Thr	gtt Val	cct Pro 125	gly aaa	gcc Ala	cgg Arg	562
gat Asp	gga Gly 130	cat His	tca Ser	gcc Ala	tgt Cys	gtc Val 135	cta Leu	ggc Gly	aag Lys	atc Ile	atg Met 140	tac Tyr	att Ile	ttt Phe	Gly 999	610
	Tyr				gcg Ala 150											658
gat Asp	acc Thr	agc Ser	acc Thr	atg Met 165	aca Thr	tgg Trp	act Thr	ctt Leu	atc Ile 170	tgt Cys	aca Thr	aag Lys	ggc Gly	agc Ser 175	cct Pro	706
gca Ala	cgc Arg	tgg Trp	agg Arg 180	Asp	ttc Phe	cac His	tca Ser	gcc Ala 185	aca Thr	atg Met	ctg Leu	gga Gly	agt Ser 190	cac His	atg Met	754
tat Tyr	gtc Val	ttt Phe 195	Gly	ggc	cgt Arg	gcc Ala	gac Asp 200	Arg	ttt Phe	Gl y aaa	cca Pro	ttc Phe 205	cat His	tcc Ser	aac Asn	802
aat Asn	gag Glu 210	Ile	tac Tyr	tgc Cys	aac Asn	cgc Arg 215	Ile	cga Arg	gtc Val	ttt Phe	gac Asp 220	Thr	aga Arg	act Thr	gag Glu	850
	Trp		Asp	Cys		Pro					Pro				cgg Arg 240	898
					Gly					Leu					ggt Gly	946
				Leu					His					Phe	aat Asn	994
			Phe					Ile					Lys		cca Pro	1042
_		Arg		_	_	_	Cys	_		-		Asp	_		gtc Val	1090
cto	ttt	ggg	ggt	acc	agt	сса	tct	cct	gag	gaa	ggo	ctg	gga	gat	gaa	1138

WO 01/55437		PCT/US01	/02623
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aag ccc cgg gcc cca Lys Pro Arg Ala Pro 115	Gly Asp Glu Glu Ala	cag gtg gag aac ctc atc Gln Val Glu Asn Leu Ile 125	505
	gag ccc cag aaa gca Glu Pro Gln Lys Ala 135	gag aac tga agtgcagcca Glu Asn *	554
tcaggtggaa gcctctgg	aa cctgaggcgg ctgctt	gaac ctttggatgc aaatgtcgat	614
gcttaagaaa accggcca	ct tcagcaacag cccttte	cccc aggagaagcc aagaacttgt	674
gtgtccccca ccctatcc	cc tctaacacca ttcctc	cacc tgatgatgca actaacactt	734
geeteeceae tgeageet	gc ggtcctgccc acctcc	cgtg atgtgtgtgt gtgtgtgtgt	794
gtgtgtgact gtgtgtgt	tt gctaactgtg gtctttg	gtgg ctacttgttt gtggatggta	854
ttgtgtttgt tagtgaac	tg tggactcgct ttcccag	ggca ggggctgagc cacatggcca	914

tetgeteete eetgeeeetg tgggeeetee ateacettet geteetagga ggetgettgt tgeeegagaa eeageeeeet eeentgattt taggggatgg egtaggggta aggageaagg

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1034

1062

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WO 01/55437		PCT/US01/02623
aga ggt gac tgg gcc tgg tgc c Arg Gly Asp Trp Ala Trp Cys G 295	ln Arg Cys Pro Leu Val	
tcc gtc agc aga gcc cca agt c Ser Val Ser Arg Ala Pro Ser P 310 3		
tcg gag caa cct tca aga gat c Ser Glu Gln Pro Ser Arg Asp L 325 330	_	J J
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acacatgtgg atcctcgttt tccaaga	aaa aaaaaa	1400

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													_		
													cag Gln 50		440
				Leu									cac His		488
													gag Glu		536
													ttg Leu		584
			-			_	_		 -		_		ttt Phe		632
													aat Asn 130		680
													cca Pro		728
													tcc Ser		776
	-	-		_			_		_		-		cac His	_	824
_					-			_					ttc Phe		872
													att Ile 210		920
				_									tac Tyr		968
				•	•					-	•	•	acg Thr	_	1016
			-		_		_					-	ttc Phe	_	1064
					_	_	_		_				ctg Leu	_	1112
													tgg Trp 290		1160

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ccc cct tgg gaa tgg ggt agt gag gcc cca gac ttc acc ccc agc cca Pro Pro Trp Glu Trp Gly Ser Glu Ala Pro Asp Phe Thr Pro Ser Pro 370 375 380	1211
ctg cta aaa tct gtt ttc tga ca gatgggtttt ggggagtcgc ctgctgcact Leu Leu Lys Ser Val Phe * 385	1264
acatgagaaa gggactccca tttgcccttc cctttctcct acagtccctt ttgtcttgtc	1324
tgtcctgggc tgtctgtgtg tgtgccattc tctggacttc agagccccct gagccagtcc	1384
tecettecca geeteeettt gggeeteeet aacteeaeet aggetgeeag ggaeeggagt	1444
cagetggtte aaggecateg ggagetetge etccaagtet accetteeet teeeggaete	1504
cetectgtee cetectttee tecetectte ettecaetet cetteetttt getteeetge	1564
cotttecce tecteaggtt etteceteet teteactggt ttttecacet tecteettee	1624
cttcttccct ggctcctagg ctgtgatata tatttttgta ttatctcttt cttctttg	1684
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<213> Homo sapiens

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W	0 01/3	53437													PC 1/C	301/02023
			_	_	-			_			tct Ser	_				443
	_	_				-					ctc Leu	-				491
											Gly aaa					539
											999 Gly 170					587
											atc Ile					635
											tgc Cys					683
cag Gln	aag Lys	cga Arg	cgc Arg 210	aga Arg	ccc Pro	tca Ser	gly aaa	cag Gln 215	caa Gln	ggt Gly	gcc Ala	ctg Leu	agg Arg 220	cag Gln	gag Glu	731
											gct Ala					779
											cct Pro 250					827
ccc Pro 255	cga Arg	gjå aaa	gga Gly	ccc Pro	cgg Arg 260	cct Pro	gjå aaa	atg Met	ccc Pro	cac His 265	ccc Pro	aag Lys	gjà aaa	gct Ala	cca Pro 270	875
gcc Ala	ttc Phe	cag Gln	ttg Leu	aac Asn 275	cgc Arg	tca Ser	ctc Leu	agt Ser	ggt Gly 280	cag Gln	cgt Arg	ttc Phe	ctg Leu	cac His 285	act Thr	923
tta Leu	cct Pro	ctc Leu	atg Met 290	tgc Cys	gtt Val	tcc Ser	cgg Arg	cct Pro 295	gat Asp	gtt Val	gtg Val	gtg Val	gtg Val 300	tgc Cys	ggc Gly	971
gtg Val	ctc Leu	act Thr 305	ctc Leu	tcc Ser	ctc Leu	atg Met	aac Asn 310	acc Thr	cac His	cca Pro	cct Pro	cgt Arg 315	ttc Phe	cgc Arg	agc Ser	1019
ccc Pro	tgc Cys 320	atg Met	ctg Leu	ctc Leu	cag Gln	agg Arg 325	tgg Trp	gtg Val	gga Gly	ggt Gly	gag Glu 330	ctg Leu	gly ggg	gct Ala	cct Pro	1067
tgg Trp 335	gcc Ala	ctc Leu	atc Ile	ggt Gly	cat His 340	ggt Gly	ctc Leu	gtc Val	cca Pro	ttc Phe 345	cac His	acc Thr	att Ile	tgt Cys	ttc Phe 350	1115
tct Ser	gtc Val	tcc Ser	cca Pro	tcc Ser 355	tac Tyr	tcc Ser	aag Lys	gat Asp	gcc Ala 360	ggc Gly	atc Ile	acc Thr	ctg Leu	agg Arg 365	gct Ala	1163

acg tgg tgt gaa ctg aga ggt gat gag atg cgt aga tca tct gcc ccc Thr Trp Cys Glu Leu Arg Gly Asp Glu Met Arg Arg Ser Ser Ala Pro 30 35 40	509
tgc ctg gtg ggc agc cct ggc ccc acg tgc tga cccaggca cagaaaagcc Cys Leu Val Gly Ser Pro Gly Pro Thr Cys * 45 50	560
acatacgtgt actgggcacg ctctatggaa gaacggtgaa ttgttgctct ggcaaataat	620
atccagcaga gatcagtggg cccagggtgc actggtaaga aatgggttcc agtcgattcc	680
tgtgtggttt tgaggatcat ggtgagctag gatctaccaa agcagctgtt tacaaagtgg	740
tgaccatgct gacagcagac tcaagagagg gtgtggggcc gggtgcggtg gctcacgcct	800
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gaa	863
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Met Glu Ser Arg Met Trp Pro Ala Leu Leu Leu Ser His Leu

1 5 10

60

ctc cct ctc tgg cca ctg ctg ttg ctg ccc ctc cca ccg cct gct cag
Leu Pro Leu Trp Pro Leu Leu Leu Pro Leu Pro Pro Pro Ala Gln
15 20 25 30

gac tot toa toe toe cot oga acc coa coa goo coa goo coc cog
Asp Ser Ser Ser Ser Pro Arg Thr Pro Pro Ala Pro Ala Arg Pro Pro
35
40
45

tgt gcc agg gga ggc ccc tcg gcc cca cgt cat gtg tgc gtg tgg gag 251 Cys Ala Arg Gly Gly Pro Ser Ala Pro Arg His Val Cys Val Trp Glu 50 55 60

cga gca cct cca cca agc cga tct cct cgg gtc cca aga tca cgt cgg 299
Arg Ala Pro Pro Pro Ser Arg Ser Pro Arg Val Pro Arg Ser Arg Arg
65 70 75

caa gtc ctg cct ggc act gca ccc cca gcc acc cca tca ggc ttt gag
Gln Val Leu Pro Gly Thr Ala Pro Pro Ala Thr Pro Ser Gly Phe Glu
80
85
90

gag ggg ccg ccc tca tcc caa tac ccc tgg gct atc gtg tgg ggt ccc
Glu Gly Pro Pro Ser Ser Gln Tyr Pro Trp Ala Ile Val Trp Gly Pro
95 100 105 110

w	01/5	5437												]	PCT/US	501/02623
	tat Tyr 10										_	_			_	100
_	tgt Cys	_					-						_			148
_	ggc		_	_	_					_	_		_			196
_	gct Ala	_	_	_								_			_	244
	att Ile						tc (	cagco	gagg	aa a	gttc	ccac	c acq	gati	tee	297
ttt	cagg	ggc <sup>†</sup> t	tccca	attgo	a tt	act	ggaca	a act	tota	aact	atte	gaaa	att 1	ttcca	attggg	357
agaa	attct	cc g	gtgt	gtcai	ct tt	tete	gtagt	tec	att	aat	gcas	gtgat	ag t	tati	tttta	417
tctt	cctgt	gt t	tttc	cta	ct to	cctga	attaa	a att	atga	acct	cct	caaat	gg a	aaggg	gcaata	a 477
taaa	actca	att t	tatti	tta	t at	ccca	acagt	aat	tgto	cagg	ctca	agact	tc t	ctgt	gagca	a 537
tcad	ccgad	ctg a	acca	gggta	ac cg	gctgg	gctgg	g gat	gtta	acat	ggag	gcagt	tta d	cacta	agcatt	597
ttag	gttt	caa a	atgga	atgca	ag at	tcag	gc									624

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<222> (387)..(542)

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ggggatggat ctctcgcctc tgcgttcaag ggggcaaatc tccaggataa atgccccctt 180
ttcctacacc attttccacc agccttggag agtcagcttc ccatggcttc cttccaacgg 240

aagçaggaga aagggctggg ctagttaaac cgcagcactt tcagttttag ggtgtgtcgt 300

gtaggttagt gatttgtgct ctgcagagac tctccaggga gagcaaaaag agcaggtgga 360

atcatcaget tggccagaag acgcag atg acg ccc cgt gag cca gct cag gaa 41

Met Thr Pro Arg Glu Pro Ala Gln Glu

aga cgg ccc cac ctt gaa ggg ccc acg ctg aaa gcc agt gat ggg gag Arg Arg Pro His Leu Glu Gly Pro Thr Leu Lys Ala Ser Asp Gly Glu 10 25

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<221> CDS

<222> (29)..(265)

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cccccccca	ggggggttt	tggcgacatc	C			810

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gtttccttcc ttttagaccg acatttggtt gggactggtt ttaactacct tgaggacttt	180
tettatetea eccateteaa atgteteete eeetgtaggg tgt atg gge ate age Met Gly Ile Ser 1	239
tgc aag ttg ctt ctt ctg act aga gtc tgc tac ctg atc acc ccg tta Cys Lys Leu Leu Leu Thr Arg Val Cys Tyr Leu Ile Thr Pro Leu 5 10 15 20	283
gat ctt gag agg ttt ccc ttc cca aac act gag cag gtg aca ttt ccg Asp Leu Glu Arg Phe Pro Phe Pro Asn Thr Glu Gln Val Thr Phe Pro 25 30 35	33:
gaa cgc aga gtt agc gtc ttc ctg ctg cct ctg agc tgg tgt ttg gac Glu Arg Arg Val Ser Val Phe Leu Leu Pro Leu Ser Trp Cys Leu Asp 40 45 50	379
aca agg ctg ccc aga gag cct ggc tgc agg tgt cga cac agc tct cca Thr Arg Leu Pro Arg Glu Pro Gly Cys Arg Cys Arg His Ser Ser Pro 55 60 65	427
cag gac gtg gtt ggc ggc agt cac ctg gtc acc aca act ctt cta agc Gln Asp Val Val Gly Gly Ser His Leu Val Thr Thr Thr Leu Leu Ser 70 75 80	475
ctc cca gct cgg gaa ttc tgg acc tct tgc atc ctc taa attggatgct Leu Pro Ala Arg Glu Phe Trp Thr Ser Cys Ile Leu * 85 90 95	524
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cat agc tgc ata aag aag tct agg aac ctg agt tct aga ctt tgt gaa His Ser Cys Ile Lys Lys Ser Arg Asn Leu Ser Ser Arg Leu Cys Glu 55 60 65	727
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ggt cac ttt gtg att tcc tac ctt ccc tca ttt tct ctg aac att cag Gly His Phe Val Ile Ser Tyr Leu Pro Ser Phe Ser Leu Asn Ile Gln 20 25 30	273
gat act ctt aag tca gtt cat cag cca tgc agt gca ctg tct ggt tat Asp Thr Leu Lys Ser Val His Gln Pro Cys Ser Ala Leu Ser Gly Tyr 35 40 45	321
aac atg cct gaa aag cca gag gaa tgt tct atc aaa gag cgg cat ccc Asn Met Pro Glu Lys Pro Glu Glu Cys Ser Ile Lys Glu Arg His Pro 50 55 60 65	369
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cta ctt att act ctt caa ttc cat ttc aga gtc tgt tac gtg aac ata 301 Leu Leu Ile Thr Leu Gln Phe His Phe Arg Val Cys Tyr Val Asn Ile 65 att acc ctt atc cct ctt gca caa atc ttt ctt taa tctg ttggatgact 351 Ile Thr Leu Ile Pro Leu Ala Gln Ile Phe Leu \* 85 80 ctgaaaggat tagtttcagt ttggggcttg agctgtgtcc agacacacaa ctgctattag 411 ttoctaccat agttctacct gggtcagaag aatgagaaaa ataatcctta ctttttcctc 471 ctctatgagc aggaggtgct tactttttac tgatttgacc agctgaacat tttaagataa 531 tattcagcac tgtagatgaa gattagaaat tactgcgcaa actttaagtg agaataaaag 591 aatttgtggc gttctacgag actctaaaca cactatcttc cctattgtct ccttaattca 651 aacaagcatt tgggcttttt tetteattee actegaceee teecegaage teacegeeet 711 togecetee eegegteece cettecacce tetee 746

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aat ctc atc ttg aca tgc tgg ggg aga tgt gct gca cac cca gta gag 583 Asn Leu Ile Leu Thr Cys Trp Gly Arg Cys Ala Ala His Pro Val Glu 5 10 15

tta atg gga gtt aca gcc aaa acc aag gtg aag cet ctg ctc cca agg Leu Met Gly Val Thr Ala Lys Thr Lys Val Lys Pro Leu Leu Pro Arg 20 25 30 .35

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aag agt aag aaa too aaa act toa tgt att tac atg tto tgg tot tgt Lys Ser Lys Lys Ser Lys Thr Ser Cys Ile Tyr Met Phe Trp Ser Cys 5 10 15	283
ctc ata gga ttc ttc ttt ctc ctt aca tac cct cct tta aat ccg tac Leu Ile Gly Phe Phe Phe Leu Leu Thr Tyr Pro Pro Leu Asn Pro Tyr 20 25 30 35	331
ctc ccc cgg tct tct cca tct tgc aaa tgg cac caa tgt cca tcc tag Leu Pro Arg Ser Ser Pro Ser Cys Lys Trp His Gln Cys Pro Ser 40 45 50	379
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tgc tat aaa tgt aga tac att tct ttc tcc ttt aca ttt tcc gtc aca Cys Tyr Lys Cys Arg Tyr Ile Ser Phe Ser Phe Thr Phe Ser Val Thr 35 40 45	205
ccc tcc ggt ttc ttt gtt agc atc ctc cag tat ctt gcc cac att ctc Pro Ser Gly Phe Phe Val Ser Ile Leu Gln Tyr Leu Ala His Ile Leu 50 55 60	253

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730

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aatttgaata gttttcaaat ctcagtttta ccagtccagt	180
ctactcatct tttcagctgg tttttcattt gattttatac catttcctca c atg cat Met His 1	237
gta ctg atc aga act ccc tgc tct cta ata ctc tgc ctg gca aac tct Val Leu Ile Arg Thr Pro Cys Ser Leu Ile Leu Cys Leu Ala Asn Ser 5 10 15	285
age cae get agt eta eet gga tte tet get tea tet ttt eta ttt aag Ser His Ala Ser Leu Pro Gly Phe Ser Ala Ser Ser Phe Leu Phe Lys 20 25 30	333
gag tot tgc aga oto ott otg aat tot too ttt otg otg cat ggc ota Glu Ser Cys Arg Leu Leu Leu Asn Ser Ser Phe Leu Leu His Gly Leu 35 40 45 50	381
gaa att ctc tca ggg gca att gca ggc aaa tgc aac tca ttt tgt ttg Glu Ile Leu Ser Gly Ala Ile Ala Gly Lys Cys Asn Ser Phe Cys Leu 55 60 65	429
ttt tcc atc tct cag gga tca ctg tcc ttc aat gcc tca tgc ccg ttg Phe Ser Ile Ser Gln Gly Ser Leu Ser Phe Asn Ala Ser Cys Pro Leu 70 75 80	477
cct tga aaaccattgt ttaatatatt catctggact tttaggtgtg ggcattggaa Pro *	533
agataaatct agccccccgg gattccctct tgggccgaga gcagagattc tgccacatat	593 <sup>.</sup>
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669

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ctatagaaat gtcctgtatt ctgggatcaa tttccaaatg ctttactttt ttatttctgc 1439
aagttcaaat taatgtctta tagaagttat gagttaaata aggtatggaa tatcaaaa 1497

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gag Glu	gat Asp 75	ctg Leu	ctt Leu	tgc Cys	tgt Cys	tac Tyr 80	tct Ser	tcc Ser	atg Met	gtc Val	tct Ser 85	cgg Arg	aag Lys	aac Asn	aaa Lys	472
atc Ile 90	agg Arg	cgc Arg	aat Asn	cgg Arg	cag Gln 95	cta Leu	gag Glu	agg Arg	ctg Leu	gct Ala 100	tcc Ser	cac His	atc Ile	aag Lys	gaa Glu 105	520
ctg Leu	gag Glu	ccc Pro	aag Lys	ctg Leu 110	aag Lys	aag Lys	att Ile	ctg Leu	cag Gln 115	atg Met	aac Asn	cca Pro	agg Arg	atg Met 120	cgg Arg	568
aag Lys	ttc Phe	caa Gln	gtg Val 125	gat Asp	atg Met	acc Thr	ttg Leu	gat Asp 130	gcc Ala	aac Asn	aca Thr	gcc Ala	aac Asn 135	aac Asn	ttc Phe	616
ctc Leu	ctc Leu	att Ile 140	tct Ser	gac Asp	gac Asp	ctc Leu	agg Arg 145	agc Ser	gtc Val	cga Arg	agt Ser	ggg Gly 150	cgc Arg	atc Ile	aga Arg	664
cag Gln	aat Asn 155	cgg Arg	caa Gln	gac Asp	ctt Leu	gcc Ala 160	gag Glu	aga Arg	ttt Phe	gac Asp	gtg Val 165	tcc Ser	gtt Val	tgc Cys	atc Ile	712
ctg Leu 170	Gly	tcc Ser	cct Pro	cgc Arg	ttt Phe 175	acc Thr	tgt Cys	ggc Gly	cgc Arg	cac His 180	tgc Cys	tgg Trp	gag Glu	gtg Val	gac Asp 185	760
gtg Val	gga Gly	aca Thr	agc Ser	aca Thr 190	gaa Glu	tgg Trp	gac Asp	ctg Leu	gga Gly 195	gtc Val	tgc Cys	aga Arg	gaa Glu	tct Ser 200	gtt Val	808
cac His	cgc Arg	aaa Lys	999 Gly 205	Arg	atc Ile	cag Gln	ctg Leu	acc Thr 210	aca Thr	gag Glu	ctt Leu	gga Gly	ttc Phe 215	tgg Trp	act Thr	856
gtg Val	agt Ser	Leu 220	Arg	gat Asp	gga Gly	ggc	cgc Arg 225	Leu	tct Ser	gcc Ala	agc Ser	acc Thr 230	gtg Val	ccg Pro	ctg Leu	904
act Thr	tto Phe 235	Lev	ttc Phe	gta Val	gac Asp	cgc Arg 240	Lys	tta Leu	cag Gln	cga Arg	gtg Val 245	Gly	att Ile	ttt Phe	ctg Leu	952
gat Asp 250	Met	ggc Gly	atg Met	cag Gln	aac Asn 255	Val	Ser	ttt Phe	ttt Phe	gat Asp 260	Ala	gaa Glu	ggt Gly	ggt	tcc Ser 265	1000
cat His	gto Val	tat Tyi	aca Thr	tto Phe 270	Arg	ago Ser	gta Val	tct Ser	gct Ala 279	Glu	gag Glu	cca Pro	ctg Leu	tgc Cys 280	cca Pro	1048
ttt Phe	ttg Lev	g gct 1 Ala	cct Pro 285	Sex	att : Ile	cca Pro	cct Pro	aat Asr 290	Gly	gat Asp	caa Glr	ggt Gly	gto Val 295	Lev	agc Ser	1096
ato Ile	c tgt e Cys	cct Pro	Leu	g atg i Met	aac Asn	tca Ser	gg ( Gl <sub>y</sub> 309	Thr	act Thi	gat Asp	gct Ala	cca Pro	val	cgt Arg	cct Pro	1144
		ı Ala	c aaa a Lys		gcc	ctca	ctc	caaa	aaaa	ac a	ıaaaa	acag	ıg gt	aaga	aaat	1199

WO 01/55437	PCT/US01/02623
cta cgt gga cgt tcg gcc aag gga cca agg tg Leu Arg Gly Arg Ser Ala Lys Gly Pro Arg Tr 285 290	
tgg ctg cac cat ctg tct tca tct tcc cgc cat Trp Leu His His Leu Ser Ser Ser Ser Arg His 300 305	
aatctggaac tgcctctgtt gtgtgcctgc tgaataact	t ctatcccaga gaggccaaag 1024
tacagtggaa ggtggataac gccctccaat cgggtaact	c ccaggagagt gtcacagagc 1084
aggacagcaa ggacagcacc tacagcctca gcagcaccc	t gacgctgagc aaagcagact 1144
acgagaaaca caaagtctac gcctgcgaag tcacccatc	a gggcctgage tegecegtea 1204
caaagagctt caacagggga gagtgttaga gggagaagt	g cccccacctg ctcctcagtt 1264
ccagcettga ccccctccca teetttggge ettttgace	c ttttttccac agggggacct 1324
tacccctatt tgcggtnctt ccaggttcat cttttcaac	t tnaaccccct tettnettet 1384
tgggttttat ttattgttaa tgtttggagg aggattgat	t aaattaagtg aatttttttg 1444

1458

canctgttaa aaaa

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***	J 01/5	5457														1501/02025
								act Thr 35								148
								ctt Leu								196
								tct Ser								244
								gca Ala								292
								cag Gln								340
	_		_		_		_	ggt Gly 115		_				_	-	388
								tcc Ser								436
								aga Arg								484
	_					_		tat Tyr			_	_	_			532
				-				cag Gln			_	-		_		580
	_	_		_	_		_	tct Ser 195				Leu		_		628
								tgc Cys								676
	-	_				-	-	aaa Lys				_		_		724
								gaa Glu								772
								ttc Phe								820
_		-	_		-			tac Tyr 275	_		_			_		868

tet tae tgg ttt gta aga ett ett tet att aat aga ggt tgg aaa tag 682 Ser Tyr Trp Phe Val Arg Leu Leu Ser Ile Asn Arg Gly Trp Lys  $\,\,$   $\,$ 35 cagttatcta ggtttttaat gttggtttga taaacactga attttactta gtttgcatta 742 gagagettae tgttaactet taaacattta aatteeetgt teteagttet aatttteagt 802 gtgaaatcag gtaagataca tttgcaggtg aaaaagtttg aaatgtaaaa agataaccaa 862 attaatttaa tatttoottg ggaatttgat tactttttot gggagaggag ttotgggcaa 922 caacataaat actgttattt gtggatattt gcaggttacg tttggtcttc aaataagtca 982 acattatttt ctttcacaaa acttggtttt ctggctttct ataatttccc aattaacatt 1042 taaataaaag accaaattaa acaattaaac tttatttaat ttggtctttt gtttaaatgc 1102 tttgtggcta cctagcttac cttttcagct tttaaggaaa aaaaaaatca gaacttttta 1162 ttttggttcg gtcggagaca gcctcactct ggcacccagc ctgcaatgca agcgcgtgat 1222 cttagettae tggcaectet cettecaggg teaaaaaaat ceeettgeet aagtteeeee 1282 cctaccccat cattgggatt atagccaccg gcgccagccc agctaatttt gggtaccagg 1342 tttctcattt ccttctggtg gcgcgaaccc cggccctaag acctccctct ccggcgctaa 1402 cggggggatc cgcgacctct ccctccttgg cggccctccc cccgtctacg tctccataag 1462 tgctgcctgc ttgcgcggcc cggccgcccc acagctctgc tcccctctgg cgcgctgggc 1522 cccgtcccac tagaccgtat accttcttcc ctcgccgcct ggccctcaca ccgatcacca 1582 teccegeetg tecgegeege tgtgegeegt tetecateta etcatecee ectetetece 1642 ctattcacgc gcacggctca gtatc 1667

PCT/US01/02623

WO 01/55437

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1257

gac cag ggc cac agc cat ctg ggg gac ccc t gaggatctac ctgcccaggc

Asp Gln Gly His Ser His Leu Gly Asp Pro 395 ccattcccag ctccttgtct ggggagcctt ggctctgagc ctctagcatg gttcagtcct 1317 tqaaaqtgqc ctqttqqqtg gagggtqqaa qqtcctgtgc aggacaggga ggccaccaaa 1377 ggggctgctg tctcctgcac atccagcctc ctgcgactcc ccaatctgga tgcattacat 1437 tcaccagget ttgcaaaccc agecteccag tgeteatttg ggaatgetea tgagttacte 1497 cattcaaggg tgagggagta gggagggaga ggcaccatgc atgtgggtga ttatctgcaa 1557 geotgtttge egtgatgetg gaageetgtg ecactacate etggagtetg acaetgagee 1617 cetgegagtg acceptgagea cacagtteeg tageggggee catacgagae tegacgegeg 1677 1737 cgcaccacga ggtcccgagg gaggacactc gacggacacg agtgacggga aatgtgcatc tacactageg egegacaget agagegatga eggegaggae gtetegeage etaceageaa 1797 cqcqaaqacg tgcctcccgg cgtcgtatgg attaacaagc tccaagtagg gtgtacaacg 1857 1877 ccgcagcatg aactcccagg

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<211> 1667

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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					ttg Leu			_		_		-	_			534
					gag Glu											582
gag Glu	cag Gln	ttg Leu 185	cgc Arg	gtg Val	gtg Val	ej aaa	gaa Glu 190	gac Asp	acc Thr	aag Lys	gcc Ala	cag Gln 195	ttg Leu	ctg Leu	Gly aaa	630
ggc	gtg Val 200	gac Asp	gag Glu	gct Ala	tgg Trp	gct Ala 205	ttg Leu	ctg Leu	cag Gln	gga Gly	ctg Leu 210	cag Gln	agc Ser	cgc Arg	gtg Val	678
					cgc Arg 220											726
					atc Ile											774
	_	_		-	ccc Pro	_	_		-	_		_	_			822
_					aag Lys		_		-	-	-		_			870
	_	Gln	-		ctg Leu	_	-	_	_	_			_		-	918
	Ala				act Thr 300											966
					cgc Arg											1014
					gcc Ala											1062
					ctg Leu											1110
gcc Ala	cca Pro 360	Glu	ttt Phe	caa Gln	caa Gln	aca Thr 365	gac Asp	agt Ser	ggc Gly	aag Lys	gtt Val 370	ctg Leu	agc Ser	aag Lys	ctg Leu	1158
	Ala				gac Asp 380											1206

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tatggacctt	ttcaatatgc	aaattatgta	atggtacaaa	cgactttata	tcagtataat	673
aaagtgctta	acgattcatt	tttattgctg	cctgtccata	ccggaagctg	taaaatagaa	733
taatttaatt	tatgggaacg	actcacatct	tggaaaatga	agggggaaaa	acctgaattc	793
cctagtggcc	acctctgcca	ttagcctggg	cacttcctgg	gggacagagg	tggaaccccg	853
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<213> Homo sapiens

<220> <221> CDS <222> (37)..(1236)

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gat agc ctc cct cca cct gtc ttc tca gag cag gta atg gca agc atg
Asp Ser Leu Pro Pro Pro Val Phe Ser Glu Gln Val Met Ala Ser Met
25
30
35

gct gcc gtg ctc acc tgg gct ctg gct ctt ctt tca gcg ttt tcg gcc 198
Ala Ala Val Leu Thr Trp Ala Leu Ala Leu Ser Ala Phe Ser Ala
40 45 50

acc cag gca cgg aaa ggc ttc tgg gac tac ttc agc cag acc agc ggg
Thr Gln Ala Arg Lys Gly Phe Trp Asp Tyr Phe Ser Gln Thr Ser Gly
55 60 65 70

gac aaa ggc agg gtg gag cag atc cat cag cag aag atg gct cgc gag 294
Asp Lys Gly Arg Val Glu Gln Ile His Gln Gln Lys Met Ala Arg Glu
75 80 85

ccc gcg acc ctg aaa gac agc ctt gag caa gac ctc aac aat atg aac
Pro Ala Thr Leu Lys Asp Ser Leu Glu Gln Asp Leu Asn Asn Met Asn
90 95 100

aag ttc ctg gaa aag ctg agg cct ctg agt ggg agc gag gct cct cgg 390 Lys Phe Leu Glu Lys Leu Arg Pro Leu Ser Gly Ser Glu Ala Pro Arg 105 110 115

ctc cca cag gac ccg gtg ggc atg cgg cag ctg cag gag gag ttg
Leu Pro Gln Asp Pro Val Gly Met Arg Arg Gln Leu Gln Glu Glu Leu
120
125
130

845 850 855 860

gtacgaatca cataagggag attgtataca agttggagca atatccattt attattttgt 2775 aactttacag ttaaactagt tttagtttaa aaagaaaaaa tgcagggtga tttcttatta 2835 2895 ttatatgtta gcctgcatgg ttaaattcga caacttgtaa ctctatgaac ttagagttta ctattttaqc aqctaaaaat gcatcacata ttcatattgt tcaataatgt cctttcattt 2955 3015 qtttctqatt qttttcatcc tgatactgta gttcactgta gaaatgtggc tgctgaaact catttgattg tcatttttat ctatcctatg ttaaatggtt tgtttttaca aaataatacc 3075 3135 ttattttaat tqaaacgttt atgcttttgc caacacatct tgtaacttaa tatactagat gttaaggttg ttaatgtaca aaaaaaaaa accettatac tcacetgcgt tttcatttgt 3195 ttgacatttg tctattattg gatatcatta tcatatgaac ttgtcagtgg gaaacaaact 3255 qtctaaaaat ttatctctta cgtttaacat acaatcatgt gagatttagg cagagttcga 3315 taaattactg gcaaaaacaa aactcattta taaagatttt ctaatgttga ctttaatact 3375 3405 ctaacatggt acaaaccana tggtaaaatc

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<213> Homo sapiens

<220>

<221> CDS

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	590					595					600					
_			aat Asn		-	-		-					_	-	_	1995
			gat Asp													2043
gaa Glu	cct Pro	gag Glu	aga Arg 640	aat Asn	cat His	act Thr	cac His	aga Arg 645	agt Ser	ttg Leu	ttt Phe	tcc Ser	gtg Val 650	gag Glu	tct Ser	2091
_	_		gac Asp		_			_	-	_	_	_		_		2139
Gly			gca Ala													2187
_	_		aca Thr	_		-	-	_	_				_	_		2235
-			cat His	_	_				_			_		_		2283
			agt Ser 720													2331
			gjå aaa													2379
Ser			cag Gln													2427
			gaa Glu													2475
			tca Ser													2523
gat Asp																.2571
aca Thr	aat Asn	cct Pro 815	gga Gly	gta Val	agg Arg	cca Pro	agt Ser 820	aat Asn	cga Arg	gat Asp	ggc Gly	ccc Pro 825	tgt Cys	gag Glu	cgc Arg	2619
tgt Cys	ggt Gly 830	att Ile	gtc Val	cac His	act Thr	gcc Ala 835	cag Gln	ata Ile	cca Pro	gac Asp	act Thr 840	tgc Cys	tta Leu	gaa Glu	gta Val	2667
aca f	ctg Leu	aaa Lys	aac Asn	gaa Glu	acg Thr	agt Ser	gat Asp	gat Asp	gag Glu	gct Ala	ttg Leu	tta Leu	ctt Leu	tgt Cys	tag *	2715

ccc tgt gga ggt aac tgg ggg tgt tat act gag cag cag cgt tgt gat
Pro Cys Gly Gly Asn Trp Gly Cys Tyr Thr Glu Gln Gln Arg Cys Asp
385
390
395

Phe Asn Ala Thr Tyr Gln Val Asp Gly Phe Cys Leu Pro Trp Glu Ile

370

ggg tat tgg cat tgc cca aat gga agg gat gaa acc aat tgt acc atg
Gly Tyr Trp His Cys Pro Asn Gly Arg Asp Glu Thr Asn Cys Thr Met
400
405
410

tgc cag aag gaa gaa ttt cca tgt tcc cga aat ggt gtc tgt tat cct 1419
Cys Gln Lys Glu Glu Phe Pro Cys Ser Arg Asn Gly Val Cys Tyr Pro
415 420 425

cgt tct gat cgc tgc aac tac cag aat cat tgc cca aat ggc tca gat
Arg Ser Asp Arg Cys Asn Tyr Gln Asn His Cys Pro Asn Gly Ser Asp
430
440

gaa aaa aac tgc ttt ttt tgc caa cca gga aat ttc cat tgt aaa aac 1515 Glu Lys Asn Cys Phe Phe Cys Gln Pro Gly Asn Phe His Cys Lys Asn 450 455 460

aat cgt tgt gtg ttt gaa agt tgg gtg tgt gat tct caa gat gac tgt 1563 Asn Arg Cys Val Phe Glu Ser Trp Val Cys Asp Ser Gln Asp Asp Cys 465 470 475

ggt gat ggc agc gat gaa gaa aat tgc cca gta atc gtg cct aca aga 1611 Gly Asp Gly Ser Asp Glu Glu Asn Cys Pro Val Ile Val Pro Thr Arg 480 485 490

gtc atc act gct gcc gtc ata ggg agc ctc atc tgt ggc ctg tta ctc 1659
Val Ile Thr Ala Ala Val Ile Gly Ser Leu Ile Cys Gly Leu Leu Leu
495 500 505

gtc ata gca ttg gga tgt act tgt aag ctt tat tct ctg aga atg ttt 1707
Val Ile Ala Leu Gly Cys Thr Cys Lys Leu Tyr Ser Leu Arg Met Phe
510 520

gaa aga aga tca ttt gaa aca cag ttg tca aga gtg gaa gca gaa ttg 1755 Glu Arg Arg Ser Phe Glu Thr Gln Leu Ser Arg Val Glu Ala Glu Leu 525 530 540

tta aga aga gaa gct cct ccc tcg tat gga caa ttg att gct cag ggt
Leu Arg Arg Glu Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly
545
550
555

tta att cca cca gtt gaa gat ttt cct gtt tgt tca cct aat cag gct
Leu Ile Pro Pro Val Glu Asp Phe Pro Val Cys Ser Pro Asn Gln Ala
560
565
570

tct gtt ttg gaa aat ctg agg cta gcg gta cga tct cag ctt gga ttt
Ser Val Leu Glu Asn Leu Arg Leu Ala Val Arg Ser Gln Leu Gly Phe
575 580 585

act tca gtc agg ctt cct atg gca ggc aga tca agc aac att tgg aac 1947 Thr Ser Val Arg Leu Pro Met Ala Gly Arg Ser Ser Asn Ile Trp Asn

80 85 90

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aca Thr	ata Ile 110	gaa Glu	aca Thr	tac Tyr	aag Lys	aat Asn 115	att Ile	gaa Glu	agt Ser	tac Tyr	aga Arg 120	gct Ala	tgt Cys	ggt Gly	tcc Ser	507	
aca Thr 125	att Ile	cca Pro	cct Pro	ccg Pro	tat Tyr 130	atc Ile	tct Ser	tca Ser	caa Gln	gac Asp 135	cac His	atc Ile	tgg Trp	att Ile	agg Arg 140	555	
ttt Phe	cat His	tcg Ser	gat Asp	gac Asp 145	aac Asn	atc Ile	tct Ser	aga Arg	aag Lys 150	ggt Gly	ttc Phe	aga Arg	ctg Leu	gca Ala 155	tat Tyr	603	
ttt Phe	tca Ser	gly aaa	aaa Lys 160	tct Ser	gag Glu	gaa Glu	cca Pro	aat Asn 165	tgt Cys	gct Ala	tgt Cys	gat Asp	cag Gln 170	ttt Phe	cgt Arg	651	
Cys	Gly	Asn 175	Gly	Lys	tgt Cys	Ile	Pro 180	Glu	Ala	Trp	Lys	Сув 185	Asn	Asn	Met	699	
gat Asp	gaa Glu 190	tgt Cys	gga Gly	gat Asp	agt Ser	tcc Ser 195	gat Asp	gaa Glu	gag Glu	atc Ile	tgt Cys 200	gcc Ala	aaa Lys	gaa Glu	gca Ala	747	
					gct Ala 210											795	
•	_			_	ttt Phe			_								843	
					aac Asn											891	
					aca Thr											939	
					aat Asn			-						_		987	
					gac Asp 290											1035	
		_			ctt Leu	_						_		_		1083	
					gag Glu											1131	
					cat His											1179	

100 105 110

gca ttg aaa gaa tgt cta act gct taa tacct gaaggaaaat atctctgaga 629 Ala Leu Lys Glu Cys Leu Thr Ala \* 115 120 cttcctccag ccttgtgatt tgttggatta atataattta actcctagaa agttgagata 689 aatcgtatgg atgataaaaa gctataatga tccagccttt tatgaagaat gcaaaatgga 749 atacctgaag gaaagggaag aattcagaaa aactggaatt cctacaaaga aaaggctaca 809 869 gaagetteca acaageatgt aggeagatac teaaatgaca tteaggaact etaatattea tggaagtcat tttatagtcc ttaaataatg gactcaagca tatatgtttg ctttacctta 929 attatggaaa tattaacttt atctgaaata aatattttat ttgtaaacgc ggccgcgaat 989 teggateete gagagatete tttttttggg tttggtgggg tatetteate gteg 1043

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411

age tgg tte ata agg gea aac eea gge gaa ate att aet ata agt ttt

Ser Trp Phe Ile Arg Ala Asn Pro Gly Glu Ile Ile Thr Ile Ser Phe

aggtgtcaga ctgcaggaaa ggagctcact ctgctggggt ggatatctga ggcagagatc 481
tgctggtata ggggaccaac tggctaagta agtttcccca agactcacgg aatttccaca 541
acaggtgatt taggatctga aaacctgaca attatgggta cacatgaggg gggcagcctg 601
cacaatgttc tccaggtgag gagactggtg gttgagttgc cctttgaaag gggtgggtag 661
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tcccctttct gggcccccgg c 742

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Lys Asn Ser Gly Val Leu Met Val Val Lys Cys Arg Lys Glu Asn Ser

PCT/US01/02623 WO 01/55437 Phe Asn Cys Val Ser Pro Gly Ile Leu Pro Ile Ser Leu Cys Leu Ala ttc aat cat gat aga agc acc ttt ttc ttt tca ata ata tta ttg tta 253 Phe Asn His Asp Arg Ser Thr Phe Phe Phe Ser Ile Ile Leu Leu Leu 50 55 302 aaa gcc tta att att ttg tct tct ctg ctt caa act aag taa ttctgac Lys Ala Leu Ile Ile Leu Ser Ser Leu Leu Gln Thr Lys \* 65 362 ttccttaatc ttttatcaca ggctctgttc tccaaacttt cagtcttttc tgttggtcca tattccattq qtttctcctc ctactcattc agaggcaaat taaggtggtt ttttaagttt 422 482

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cgaaaggate aaggegaceg geggeeecea eeeetegggg gettetetta aeggetgtgg 662
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421

tgaggaatcc atgccatgag gagtttatgg tctgtgaaga atacaggcag gaatttgaga